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NEWS 7 Mar 22 TOXLIT no longer available
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NEWS 9 Mar 28 US Provisional Priorities searched with P in CA/CAPLUS
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NEWS 21 Jun 10 PCTFULL has been reloaded
NEWS 22 Jul 02 FOREGE no longer contains STANDARDS file segment

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=> file medline caplus embase biosis			
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=> s (nef (1N) (84-92)) or (GAG (1N) 77-85)
L1 20 (NEF (1N) (84-92)) OR (GAG (1N) 77-85)

=> dup rem l1
PROCESSING COMPLETED FOR L1
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)

=> dis l2 ibib abs 1-5

L2 ANSWER 1 OF 5	MEDLINE	DUPLICATE 1
ACCESSION NUMBER:	2002216247	IN-PROCESS
DOCUMENT NUMBER:	21948637	PubMed ID: 11952141
TITLE:	Differential processing of HLA A2-restricted HIV type 1 cytotoxic T lymphocyte epitopes.	
AUTHOR:	Sewell Andrew K; Booth Bruce L Jr; Cerundolo Vincenzo; Phillips Rodney E; Price David A	
CORPORATE SOURCE:	Nuffield Department of Clinical Medicine, John Radcliffe Hospital, Oxford, United Kingdom.. andy.sewell@ndm.ox.ac.uk	
SOURCE:	VIRAL IMMUNOLOGY, (2002) 15 (1) 193-6. Journal code: 8801552. ISSN: 0882-8245.	
PUB. COUNTRY:	United States	
LANGUAGE:	English	
FILE SEGMENT:	IN-PROCESS; NONINDEXED; Priority Journals	
ENTRY DATE:	Entered STN: 20020416 Last Updated on STN: 20020416	

AB Cytotoxic T lymphocytes (CTLs) play a key role in the control of
persistent viral infections. Differences in the quality of this cellular
immune response influence the long-term outcome of such infections, but
the factors that determine which virus-derived peptide epitopes are

targeted by CTLs remain poorly understood. Here, we examine the antigen-processing requirements of three human leukocyte antigen (HLA) A*0201-restricted HIV-1 CTL epitopes. Each of these three peptides appears to be generated by a distinct proteolytic pathway, despite presentation on the cell surface in association with the same HLA class I molecule. Presentation of the commonly immunodominant SLYNTVATL (HIV-1 p17 Gag; residues 77-85) epitope was unaffected by inhibition of the proteasome with lactacystin, but was dependent on the presence of the beta-subunit LMP7. These findings are consistent with emerging data on the complexity of peptide epitope generation, and suggest that differences in antigen processing might contribute to patterns of CTL recognition in vivo.

L2 ANSWER 2 OF 5 MEDLINE DUPLICATE 2
 ACCESSION NUMBER: 2001256877 MEDLINE
 DOCUMENT NUMBER: 21067100 PubMed ID: 11148222
 TITLE: Substantial differences in specificity of HIV-specific cytotoxic T cells in acute and chronic HIV infection.
 AUTHOR: Goulder P J; Altfeld M A; Rosenberg E S; Nguyen T; Tang Y; Eldridge R L; Addo M M; He S; Mukherjee J S; Phillips M N; Bunce M; Kalams S A; Sekaly R P; Walker B D; Brander C
 CORPORATE SOURCE: Partners AIDS Research Center, Massachusetts General Hospital and Harvard Medical School, Charlestown, Massachusetts 02129, USA.. goulder@helix.mgh.harvard.edu
 CONTRACT NUMBER: A101541 (NIAID)
 A128568 (NIAID)
 A146995 (NIAID)
 SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (2001 Jan 15) 193 (2) 181-94.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200105
 ENTRY DATE: Entered STN: 20010521
 Last Updated on STN: 20010521
 Entered Medline: 20010517

AB Cytotoxic T lymphocytes (CTLs) play a vital part in controlling viral replication during human viral infections. Most studies in human infections have focused on CTL specificities in chronic infection and few data exist regarding the specificity of the initial CTL response induced in acute infection. In this study, HIV-1 infection in persons expressing human histocompatibility leukocyte antigen (HLA)-A*0201 was used as a means of addressing this issue. In chronic infection, the dominant HLA-A*0201-restricted CTL response is directed towards the epitope SLYNTVATL ("SL9") in p17 Gag (residues 77-85). This epitope is targeted by 75% of HLA-A*0201-positive adults, and the magnitude of this A*0201-SL9 response shows a strong negative association with viral load in progressive infection. Despite using the highly sensitive peptide-major histocompatibility complex tetramer and intracellular cytokine assays, responses to the SL9 epitope were not detectable in any of 11 HLA-A*0201-positive subjects with acute HIV-1 infection ($P = 2 \times 10^{-6}$), even when assays were repeated using the SL9 peptide variant that was encoded by their autologous virus. In contrast, multiple responses (median 3) to other epitopes were evident in 7 of the 11 A*0201-positive subjects. Longitudinal study of two subjects confirmed that the A*0201-SL9 response emerged later than other CTL responses, and after viral set point had been reached. Together, these data show that the CTL responses that are present and that even may dominate in chronic infection may differ substantially from those that constitute the initial antiviral CTL response. This finding is an important consideration in vaccine design and in the evaluation of vaccine candidates.

L2 ANSWER 3 OF 5 MEDLINE DUPLICATE 3
 ACCESSION NUMBER: 2001548908 MEDLINE
 DOCUMENT NUMBER: 21479466 PubMed ID: 11595297
 TITLE: Mother-to-child transmission of HIV infection and CTL escape through HLA-A2-SLYNTVATL epitope sequence variation.
 AUTHOR: Goulder P J; Pasquier C; Holmes E C; Liang B; Tang Y; Izopet J; Saune K; Rosenberg E S; Burchett S K; McIntosh K; Barnardo M; Bunce M; Walker B D; Brander C; Phillips R E
 CORPORATE SOURCE: Department of Paediatrics, Nuffield Department of Medicine, Level 7, Room 7615, John Radcliffe Hospital, Oxford OX3 9DU, UK.. philip.goulder@ndm.ox.ac.uk
 CONTRACT NUMBER: A1 01541 (NIAID)
 A128568 (NIAID)
 A130914 (NIAID)
 A146995 (NIAID)
 SOURCE: IMMUNOLOGY LETTERS, (2001 Nov 1) 79 (1-2) 109-16.
 PUB. COUNTRY: Netherlands
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200202
 ENTRY DATE: Entered STN: 20011015
 Last Updated on STN: 20020209
 Entered Medline: 20020208

AB Cytotoxic T lymphocytes (CTL) play a central role in containment of HIV infection. Evasion of the immune response by CTL escape is associated with progression to disease. It is therefore hypothesised that transmitted viruses encode escape mutations within epitopes that are required for successful control of viraemia. In order to test this hypothesis, escape through the dominant HLA-A2-restricted CTL epitope SLYNTVATL (p17 Gag residues 77-85 SL9) in the setting of mother-to-child-transmission (MTCT) was investigated. Initial data from two families in which the HIV-infected mother expressed HLA-A*0201 and had transmitted the virus to other family members were consistent with this hypothesis. In addition, analysis of the gag sequence phylogeny in one family demonstrated that CTL escape variants can be successfully transmitted both horizontally and vertically. To test the hypothesis further, a larger cohort of transmitting mothers (n=8) and non-transmitters (n=14) were studied. Variation within the SL9 epitope was associated with expression of HLA-A2 ($P=0.04$) but overall no clear link between variation from the SL9 consensus sequence and MTCT was established. However, the high level of background diversity within p17 Gag served to obscure any possible association between escape and MTCT. In conclusion, these studies highlighted the obstacles to demonstrating CTL escape arising at this particular epitope. Alternative strategies likely to be more definitive are discussed.

L2 ANSWER 4 OF 5 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 1998282291 MEDLINE
DOCUMENT NUMBER: 98282291 PubMed ID: 9616227
TITLE: Lack of strong immune selection pressure by the immunodominant, HLA-A*0201-restricted cytotoxic T lymphocyte response in chronic human immunodeficiency virus-1 infection.
AUTHOR: Brander C; Hartman K E; Trocha A K; Jones N G; Johnson R P; Korber B; Wentworth P; Buchbinder S P; Wolinsky S; Walker B D; Kalams S A
CORPORATE SOURCE: AIDS Research Center and Infectious Disease Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA.
CONTRACT NUMBER: R01 AI 33327 (NIAID)
R01 AI30914 (NIAID)
R37 AI28568 (NIAID)
SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1998 Jun 1) 101 (11) 2559-66.
Journal code: 7802877. ISSN: 0021-9738.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199806
ENTRY DATE: Entered STN: 19980713
Last Updated on STN: 19980713
Entered Medline: 19980626
AB Despite detailed analysis of the HIV-1-specific cytotoxic T lymphocyte response by various groups, its relation to viral load and viral sequence variation remains controversial. We analyzed HLA-A*0201 restricted cytotoxic T lymphocyte responses in 17 HIV-1-infected individuals with viral loads ranging from < 400 to 221,000 HIV RNA molecules per milliliter of plasma. In 13 out of 17 infected subjects, CTL responses against the SLYNTVATL epitope (p17 Gag; aa 77-85) were detectable, whereas two other HLA-A*0201 restricted epitopes (ILKEPVHGV, IV9; and VIQYMDDL, VL9) were only recognized by six and five individuals out of 17 individuals tested, respectively. Naturally occurring variants of the SL9 epitope were tested for binding to HLA-A*0201 and for recognition by specific T cell clones generated from five individuals. Although these variants were widely recognized, they differed by up to 10,000-fold in terms of variant peptide concentrations required for lysis of target cells. A comparison of viral sequences derived from 10 HLA-A*0201-positive individuals to sequences obtained from 11 HLA-A*0201-negative individuals demonstrated only weak evidence for immune selective pressure and thus question the in vivo efficacy of immunodominant CTL responses present during chronic HIV-1 infection.

L2 ANSWER 5 OF 5 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 95016420 MEDLINE
DOCUMENT NUMBER: 95016420 PubMed ID: 7523570
TITLE: Naturally processed viral peptides recognized by cytotoxic T lymphocytes on cells chronically infected by human immunodeficiency virus type 1.
AUTHOR: Tsomides T J; Aldovini A; Johnson R P; Walker B D; Young R A; Bisen H N
CORPORATE SOURCE: Center for Cancer Research, Massachusetts Institute of Technology, Cambridge 02139.
CONTRACT NUMBER: AI-26463 (NIAID)
AI-34247 (NIAID)
R35 CA-42504 (NCI)
SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Oct 1) 180 (4) 1283-93.
Journal code: 2985109R. ISSN: 0022-1007.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199411
ENTRY DATE: Entered STN: 19941222
Last Updated on STN: 19960129
Entered Medline: 19941102

AB We have established long-term cultures of several cell lines stably and uniformly expressing human immunodeficiency virus type 1 (HIV-1) in order to (a) identify naturally processed HIV-1 peptides recognized by cytotoxic T lymphocytes (CTL) from HIV-1-seropositive individuals and (b) consider the hypothesis that naturally occurring epitope densities on HIV-infected cells may limit their lysis by CTL. Each of two A2-restricted CD8+ CTL specific for HIV-1 gag or reverse transcriptase (RT) recognized a single naturally processed HIV-1 peptide in trifluoroacetic acid (TFA) extracts of infected cells: gag 77-85 (SLYNTVATL) or RT 476-484 (ILKEPVHGV). Both processed peptides match the synthetic peptides that are optimally active in cytotoxicity assays and have the consensus motif described for A2-associated peptides. Their abundances were approximately 400 and approximately 12 molecules per infected Jurkat-A2 cell, respectively. Other synthetic HIV-1 peptides active at subnanomolar concentrations were not present in infected cells. Except for the antigen processing mutant line T2, HIV-infected HLA-A2+ cell lines were specifically lysed by both A2-restricted CTL, although infected Jurkat-A2 cells were lysed more poorly by RT-specific CTL than by gag-specific CTL, suggesting that low cell surface density of a natural peptide may limit the effectiveness of some HIV-specific CTL despite their vigorous activity against synthetic peptide-treated target cells.

=> s analogue
L3 207502 ANALOGUE

=> s 12 and 13
L4 0 L2 AND L3

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002

L1 20 S (NEP (1N) (84-92)) OR (GAG (1N) 77-85)

L2 5 DUP REM L1 (15 DUPLICATES REMOVED)

L3 207502 S ANALOGUE

L4 0 S L2 AND L3

=> s 11 and 13

L5 0 L1 AND L3

=>

=> s 13 and HIV
L6 4675 L3 AND HIV

=> s 13 (P) (peptide? or protein?)
L7 46831 L3 (P) (PEPTIDE? OR PROTEIN?)

=> s 17 (P) AIDS
L8 184 L7 (P) AIDS

=> s 17 (P) (HIV or NEF or AIDS)
L9 801 L7 (P) (HIV OR NEF OR AIDS)

=> s 17 (P) (HIV or NEF or AIDS or GAG)
L10 847 L7 (P) (HIV OR NEF OR AIDS OR GAG)

=> s 17 (P) (NEF or GAG)
L11 110 L7 (P) (NEF OR GAG)

=> s 111 and PD<19980507
'19980507' NOT A VALID FIELD CODE
3 FILES SEARCHED...
L12 64 L11 AND PD<19980507

=> dup rem 112
PROCESSING COMPLETED FOR L12
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)

=> dis 113 1-41 ibib abs

L13 ANSWER 1 OF 41 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:490879 BIOSIS
DOCUMENT NUMBER: PREV199800490879
TITLE: RNA structure inhibits the TRAP (trp RNA-binding
attenuation protein)-RNA interaction.
AUTHOR(S): Xirasagar, Sandhya; Elliott, Matthew B.; Bartolini, Wilmin;
Gollnick, Paul; Gottlieb, Philip A. (1)
CORPORATE SOURCE: (1) Dep. Biol. Sci., State Univ. N.Y. Buffalo, Buffalo, NY
14260 USA
SOURCE: Journal of Biological Chemistry, (Oct. 16, 1998)
Vol. 273, No. 42, pp. 27146-27153.
ISSN: 0021-9258.
DOCUMENT TYPE: Article
LANGUAGE: English
AB TRAP (trp RNA-binding Attenuation protein) regulates expression
of the tryptophan biosynthetic genes in response to tryptophan in *Bacillus*
subtilis by binding to two sites containing a series of 9 or 11 (G/U)AG
triplet repeats that are generally separated by two or three spacer
nucleotides. Previous mutagenesis experiments have identified three TRAP
residues, Lys-37, Lys-56, and Arg-58 that are essential for RNA binding.
The location of these residues on the TRAP oligomer supports the proposal
that RNA binds TRAP by encircling the TRAP oligomer. In this work, we show
that RNAs containing 11 GAG or UAG repeats separated by CC
dinucleotide spacers ((G/U)AGCC)11 form stable structures that inhibit
binding to TRAP. This conclusion is based on the effects of temperature
and Mg2+ on the affinity of TRAP for RNAs with CC spacers combined with UV
hyperchromicity and circular dichroism. Furthermore, introducing the base
analogue 7-deazaguanosine in the ((G/U)AGCC)11 RNAs stabilized the
TRAP-RNA interaction. This effect was associated with decreased stability
of the RNA structure as measured by circular dichroism spectroscopy. The
precise nature of the structure of the ((G/U)AGCC)11 RNAs is not known but
evidence is presented that it involves noncanonical interactions. We also
observed that substitution of Arg-58 with Lys further reduced the ability
of TRAP to interact with structured RNAs. Since in vivo function of TRAP
may involve binding to structured RNAs, we suggest a potential function
for this residue, which is conserved in TRAP from three different bacilli.

L13 ANSWER 2 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 1998117456 EMBASE
TITLE: Serological detection of attenuated HIV-1 variants with nef
gene deletions.
AUTHOR: Greenway AL.; Mills J.; Rhodes D.; Deacon N.J.; McPhee D.A.
CORPORATE SOURCE: D.A. McPhee, ACBU, National Ctr. HIV Virology Res.,
Macfarlane Burnet Ctr. Medical Res., PO Box 254, Fairfield,
Vic 3078, Australia
SOURCE: AIDS, (16 Apr 1998) 12/6 (555-561).
Refs: 24
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To investigate whether members of a transfusion-linked cohort
(the Sydney Bloodbank Cohort) infected with a nef-deleted strain
of HIV-1 could be differentiated from individuals infected with wild-type
strains of HIV-1 by characterizing the Nef antibody response of
cohort members. Design: Retrospective and prospective analysis of the
nef gene sequence and the antibody response to Nef
peptides in HIV-infected subjects. Methods: Plasma was obtained
from all individuals of the Sydney cohort, and from a variety of
HIV-1-infected and uninfected controls. Antibodies recognizing full-length
recombinant HIV-1(NL43) Nef protein and synthetic
peptide analogues were assessed by enzyme-linked
immunosorbent assay. Results: All 34 individuals infected with wild-type
HIV-1 had antibodies reacting with full-length Nef
protein as well as with a series of synthetic peptides
(6-23-mers) spanning most of the Nef protein of
HIV-1(NL43). Although the HIV-1 quasiespecies infecting the Sydney cohort
had a consensus deletion of the nef gene corresponding to
amino-acids 165-206, HIV-1 strains from individual members of the cohort
had additional deletions comprising up to 80% of the nef gene.
Members of the cohort had antibodies to peptides homologous to
all regions of the Nef protein tested, except for a
single peptide (amino-acids 162-177) that lies within the
consensus nef deletion for the cohort quasiespecies. Conclusion:
These data show that nef-deleted strains of HIV-1 can be
detected serologically. In the Sydney cohort, detection of antibodies to
all regions of Nef tested, except that corresponding to
amino-acids 162-177, suggests that observed deletions outside this domain

occurred after this virus had infected these subjects and stimulated an immune response. A Hef peptide serological assay may be useful for identifying further examples of individuals infected with nef-deleted, attenuated HIV-1 quasiespecies and for assessing the evolution of those variants in vivo.

L13 ANSWER 3 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 2
 ACCESSION NUMBER: 1998092248 EMBASE
 TITLE: Immune response to recombinant visna virus Gag and Env precursor proteins synthesized in insect cells.
 AUTHOR: Rafnar B.; Tobin G.J.; Nagashima K.; Gonda M.A.; Gunnarsson E.; Andresson S.; Georgsson G.; Torsteinsdottir S.
 CORPORATE SOURCE: B. Rafnar, Institute for Experimental Pathology, University of Iceland, Keldur, IS-112 Reykjavik, Iceland
 SOURCE: Virus Research, (1998) 53/2 (107-120).
 Refs: 54
 ISSN: 0168-1702 CODEN: VIREDF
 S 0168-1702(97)00141-X
 PUBLISHER IDENT.: Netherlands
 COUNTRY: Netherlands
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Two different recombinant visna virus (VV) gag-baculoviruses were constructed for the expression of precursor VV Gag in insect cells. Both recombinant Gag viruses expressed proteins migrating on SDS-PAGE at the predicted rate for VV Gag precursor, Pr50(gag). However, differences were seen in the morphology of the virus-like particles produced. Monoclonal antibody directed against the VV Gag capsid protein (p25) and sera from sheep infected with ovine lentiviruses reacted to both 50-kDa proteins. A recombinant VV env-baculovirus was constructed, substituting sequences encoding the signal peptide of VV Env with the murine IPN-gamma. analogue. Sera from ovine lentivirus infected sheep reacted in immunoblots with two proteins of approximately 100 and 200 kDa found in the plasma membrane of insect cells infected with env-recombinant virus. Sheep immunized with either the recombinant Gag or the Env proteins developed high antibody titers to VV in ELISA. The serum of sheep and ascitic fluid of mice immunized with the recombinant Gag reacted with native Pr50(gag) and the processed Gag proteins in immunoblots, whereas serum of the recombinant Env immunized sheep reacted with VV gp135 and a putative oligomer of gp135. The immunized sheep responded specifically to visna virus by lymphocyte proliferation in vitro. Copyright (C) 1998 Elsevier Science B.V.

L13 ANSWER 4 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 3
 ACCESSION NUMBER: 97309508 EMBASE
 DOCUMENT NUMBER: 1997309508
 TITLE: Transfer of the HIV-1 cyclophilin-binding site to simian immunodeficiency virus from Macaca mulatta can confer both cyclosporin sensitivity and cyclosporin dependence.
 AUTHOR: Bukovsky A.A.; Weimann A.; Accola M.A.; Gottlinger H.G.
 CORPORATE SOURCE: A.A. Bukovsky, Division of Human Retrovirology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, United States
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) 94/20 (10943-10948).
 Refs: 33
 ISSN: 0027-8424 CODEN: PNAS6
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB HIV-1 specifically incorporates the peptidyl prolyl isomerase cyclophilin A (CyPA), the cytosolic receptor for the immunosuppressant cyclosporin A (CsA). HIV-1 replication is inhibited by CsA as well as by nonimmunosuppressive CsA analogues that bind to CyPA and interfere with its virion association. In contrast, the related simian immunodeficiency virus SIVmac, which does not interact with CyPA, is resistant to these compounds. The incorporation of CyPA into HIV-1 virions is mediated by a specific interaction between the active site of the enzyme and the capsid (CA) domain of the HIV-1 Gag polyprotein. We report here that the transfer of HIV-1 CA residues 86-93, which form part of an exposed loop, to the corresponding position in SIVmac resulted in the efficient incorporation of C.apprx.PA and conferred an HIV-1-like sensitivity to a nonimmunosuppressive cyclosporin. HIV-1 CA residues 86-90 were also sufficient to transfer the ability to efficiently incorporate CyPA, provided that the length of the C.apprx.PA binding loop was preserved. However, the resulting SIVmac mutant required the presence of cyclosporin for efficient virus replication. The results indicate that the presence or absence of a type II tight turn adjacent to the primary CyPA-binding site determines whether CyPA incorporation enhances or inhibits viral replication. By demonstrating that CyPA-binding-site residues can induce cyclosporin sensitivity in a heterologous context, this study provides direct in vivo evidence that the exposed loop between helices IV and V of HIV-1 CA not merely constitutes a docking site for CyPA but is a functional target of this cellular protein.

L13 ANSWER 5 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 4
 ACCESSION NUMBER: 97125376 EMBASE
 DOCUMENT NUMBER: 1997125376
 TITLE: The non-immunosuppressive cyclosporin A analogue SDZ NIM 811 inhibits cyclophilin A incorporation into virions and virus replication in human immunodeficiency virus type 1-infected primary and growth-arrested T cells.
 AUTHOR: Mlynar E.; Bevec D.; Billich A.; Rosenwirth B.; Steinkasserer A.
 CORPORATE SOURCE: A. Steinkasserer, Immuno-AG, Div. Oncog. Viruses, Benatskygasse 2-6, A-1220 Vienna, Austria
 SOURCE: Journal of General Virology, (1997) 78/4 (825-835).
 Refs: 35
 ISSN: 0022-1317 CODEN: JGVIAV
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 026 Immunology, Serology and Transplantation
 029 Clinical Biochemistry
 030 Pharmacology
 037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB SDZ NIM 811 is a cyclosporin A (CaA) analogue that is completely devoid of immunosuppressive capacity but exhibits potent and selective antihuman immunodeficiency virus type 1 (HIV-1) activity. Binding to cyclophilin A, the intracellular receptor for cyclosporins, is a prerequisite for HIV-1 inhibition by cyclosporins. Cyclophilin A was demonstrated to bind to HIV-1 p24(gag) and this cyclophilin-gag interaction leads to the incorporation of cyclophilin A into HIV-1 virions. SDZ NIM 811 inhibits this protein interaction, and this is likely to be the molecular basis for its antiviral activity. Here, we show that in activated primary T cells SDZ NIM 811 interferes with two stages of the virus replication cycle: (i) translocation of pre-integration complexes into the nucleus and (ii) production of infectious virus particles. SDZ NIM 811 not only inhibits translocation of HIV-1 pre-integration complexes in primary T cells, but also in a growth-arrested T cell line. In vivo, most T lymphocytes are quiescent, but serve nevertheless as a major and inducible HIV-1 reservoir in infected individuals. Significant amounts of cyclophilin A were found to be associated with virus particles propagated in primary T cells. SDZ NIM 811 caused a strong reduction in the amount of incorporated cyclophilin A, thereby reducing infectivity. Thus, cyclophilin A seems to be necessary for HIV-1 replication in primary T cells.

L13 ANSWER 6 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97089614 EMBASE

DOCUMENT NUMBER: 1997089614

TITLE: .alpha.1-adrenoceptor activation of a non-selective cation current in rabbit portal vein by 1,2-diacyl-sn-glycerol.

AUTHOR: Helliwell R.M.; Large W.A.

CORPORATE SOURCE: R.M. Helliwell, Dept Pharmacology Clin Pharmacology, St. George's Hospital Medical School, Cranmer Terrace, London SW17 0RE, United Kingdom. r.helliwell@sgms.ac.uk

SOURCE: Journal of Physiology, (1997) 499/2 (417-428).

Refs: 37

ISSN: 0022-3751 CODEN: JPHYA7

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 002 Physiology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB 1. The transduction mechanisms involved in the activation and modulation of the noradrenaline-activated cation current (I(cat)) were investigated with whole-cell patch clamp techniques in rabbit portal vein smooth muscle cells. 2. Intracellular application of guanosine 5'-O-(3-thiotriphosphate) (GTP.gamma.S, 500.mu.M) evoked a 'noisy' inward current at -50 mV with a similar current-voltage relationship and reversal potential to the current evoked by bath application of noradrenaline (100.mu.M). Guanosine 5'-O-(2-thiodiphosphate) (GDP.beta.S, 1 mM) markedly inhibited noradrenaline-activated I(cat). 3. The phospholipase C (PLC) inhibitor U73122 inhibited the amplitude of the noradrenaline-activated I(cat) in a concentration- and time-dependent manner and the IC50 was about 180 nM. U73122 had similar effects on the cation current evoked by GTP.gamma.S. 4. Intracellular application of myo-inositol 1,4,5-trisphosphate (IP3, 100.mu.M) from the patch pipette did not activate any membrane current in cells where intracellular calcium concentration ([Ca2+](i)) was buffered to 14 nM, but subsequent addition of noradrenaline evoked I(cat). 5. Bath application of the 1,2-diacyl-sn-glycerol (DAG) analogue 1-oleoyl-2-acetyl-sn-glycerol (GAG, 10.mu.M) activated I(cat), whereas the phorbol ester phorbol 12,13-dibutyrate (PDBu, 0.1-5.mu.M) failed to activate I(cat), in every cell examined. I(cat) activated by GAG after bath application of PDBu was not significantly different from GAG-activated I(cat) in the absence of PDBu. The DAG lipase inhibitor RHC80267 (10.mu.M) activated I(cat) in some cells, whereas the DAG kinase inhibitor R59949 (10.mu.M) never activated I(cat). 6. Bath application of the protein kinase C inhibitor chelerythrine (1-10.mu.M) had no effect on either OAG- or noradrenaline-activated I(cat). 7. It is concluded that noradrenaline activates I(cat) via a G-protein coupled to PLC and that the resulting DAG product plays a central role in the activation of cation channels via a protein kinase C-independent mechanism.

L13 ANSWER 7 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 97086062 EMBASE

DOCUMENT NUMBER: 1997086062

TITLE: Protease inhibitors in patients with HIV disease.

Clinically important pharmacokinetic considerations.

AUTHOR: Barry M.; Gibbons S.; Back D.; Mulcahy P.

CORPORATE SOURCE: Dr. M. Barry, Department Pharmacology Therapeutics, Ashton Street Medical School, University of Liverpool, Ashton Street, Liverpool L69 3GE, United Kingdom

SOURCE: Clinical Pharmacokinetics, (1997) 32/3 (194-209).

Refs: 124

ISSN: 0312-5963 CODEN: CPKNDH

COUNTRY: New Zealand

DOCUMENT TYPE: Journal; General Review

FILE SEGMENT: 004 Microbiology

030 Pharmacology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Since its introduction in 1987, zidovudine monotherapy has been the treatment of choice for patients with HIV infection. Unfortunately it has been established that the beneficial effects of zidovudine are not sustained due to the development of resistant viral strains. This has led to the strategy of combination therapy, and in 1995 treatment with zidovudine plus didanosine, or zidovudine plus zalcitabine, was demonstrated to be more effective than zidovudine monotherapy in preventing disease progression and reducing mortality in patients with HIV disease. Recent work demonstrates an even greater antiviral effect from triple therapy with 2 nucleosides, zidovudine plus zalcitabine with the addition of saquinavir, a new protease inhibitor drug. The HIV protease enzyme is responsible for the post-translational processing of gag and gag-pol polyprotein precursors, and its inhibition by drugs such as saquinavir, zalcitabine, indinavir and VX-478 results in the production of non-infectious virions. As resistance may also develop to the protease inhibitors they may be used in combination, and future strategies may well include quadruple therapy with 2 nucleoside analogues plus 2 protease inhibitors. Administration of protease inhibitors alone or in combination with other drugs does raise a number of important pharmacokinetic issues for patients with HIV disease. Some protease inhibitors (e.g. saquinavir) have kinetic profiles characterised

by reduced absorption and a high first pass effect, resulting in poor bioavailability which may be improved by administering with food. Physiological factors including achlorhydria, malabsorption and hepatic dysfunction may influence the bioavailability of protease inhibitors in HIV disease. Protease inhibitors are very highly bound to plasma proteins (> 98%), predominantly to α_1 -acid glycoprotein. This may influence their antiviral activity in vitro and may also predispose to plasma protein displacement interactions. Such interactions are usually only of clinical relevance if the metabolism of the displaced drug is also inhibited. This is precisely the situation likely to pertain to the protease inhibitors, as ritonavir may displace other protease inhibitor drugs, such as saquinavir, from plasma proteins and inhibit their metabolism. Protease inhibitors are extensively metabolised by the cytochrome P450 (CYP) enzymes present in the liver and small intestine. In vitro studies suggest that the most influential CYP isoenzyme involved in the metabolism of the protease inhibitors is CYP3A, with the isoforms CYP2C9 and CYP2D6 also contributing. Ritonavir has an elimination half-life ($t_{1/2}$) of 3 hours, indinavir 2 hours and saquinavir between 7 and 12 hours. Renal elimination is not significant, with less than 5% of ritonavir and saquinavir excreted in the unchanged form. As patients with HIV disease are likely to be taking multiple prolonged drug regimens this may lead to drug interactions as a result of enzyme induction or inhibition. Recognised enzyme inducers of CYP3A, which are likely to be prescribed for patients with HIV disease, include rifampicin (rifampin) (treatment of pulmonary tuberculosis), rifabutin (treatment and prophylaxis of *Mycobacterium avium* complex), phenobarbital (phenobarbitone), phenytoin and carbamazepine (treatment of seizures secondary to cerebral toxoplasmosis or cerebral lymphoma). These drugs may reduce the plasma concentrations of the protease inhibitors and reduce their antiviral efficacy. If coadministered drugs are substrates for a common CYP enzyme, the elimination of one or both drugs may be impaired. Drugs which are metabolised by CYP3A and are likely to be used in the treatment of patients with HIV disease include the azole antifungals, macrolide antibiotics and dapsone; therefore, protease inhibitors may interact with these drugs. Although dapsone and cotrimoxazole (trimethoprim/sulfamethoxazole) are used in the treatment and prophylaxis of *Pneumocystis carinii* pneumonia, the incidence of adverse effects is very high, and has been attributed to the formation of a hydroxylamine metabolite mediated by CYP3A and CYP2C9 isoenzymes. The protease inhibitors, particularly ritonavir, may inhibit hydroxylamine production and reduce the incidence of adverse effects. This potential interaction may be beneficial and should be studied in the clinical setting. Protease inhibitors will be prescribed in combination with nucleoside analogues. It is unlikely that a pharmacokinetic drug interaction will result as the metabolic pathways differ. The effect of protease inhibitors on the intracellular phosphorylation of nucleoside analogues is unknown.

L13 ANSWER 8 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V. DUPLICATE 5
 ACCESSION NUMBER: 96372634 EMBASE
 DOCUMENT NUMBER: 1996372634
 TITLE: Identification of proteolytic cleavage sites within the gag-analogue protein of Tyl virus-like particles.
 AUTHOR: Martin-Rendon E.; Hurd D.W.; Marfany G.; Kingsman S.M.; Kingsman A.J.
 CORPORATE SOURCE: Department of Biochemistry, University of Oxford, South Parks Road, Oxford OX1 3QU, United Kingdom
 SOURCE: Molecular Microbiology, (1996) 22/5 (1035-1043).
 ISSN: 0950-382X CODEN: MOMIEE
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Like retroviruses, the yeast retrotransposon Tyl produces its proteins as precursors that are subsequently cleaved by a protease encoded by the element. These cleavage events are essential for transposition as they release the active reverse transcriptase and integrase and they modify the structure of the virus-like particles in a way that is analogous to the morphological changes that occur during retrovirus core maturation. Using a combination of epitope tagging, amino acid analysis and mutagenesis, we have identified the major cleavage sites for the Tyl protease within the particle-forming protein, p1, at 407S/408N. In addition, we present evidence indicating that the Tyl protease may be a 17 kDa protein.

L13 ANSWER 9 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
 ACCESSION NUMBER: 96154145 EMBASE
 DOCUMENT NUMBER: 1996154145
 TITLE: Current knowledge and future prospects for the use of HIV protease inhibitors.
 AUTHOR: Moyie G.; Gazzard B.
 CORPORATE SOURCE: Kobler Centre, Chelsea and Westminster Hospital, 369 Fulham Rd, London SW10 9TH, United Kingdom
 SOURCE: Drugs, (1996) 51/5 (701-712).
 ISSN: 0012-6667 CODEN: DRUGAY
 COUNTRY: New Zealand
 DOCUMENT TYPE: Journal; Editorial
 FILE SEGMENT: 004 Microbiology
 030 Pharmacology
 037 Drug Literature Index
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB The HIV protease (or proteinase) enzyme is an essential component of the replicative cycle of HIV, performing the post-translational processing of the gag and gag-pol gene products into the functional core proteins and viral enzymes. Inhibition of this enzyme leads to production of immature noninfectious viral progeny, and hence prevention of further rounds of infection. Structurally, the enzyme is a homodimer consisting of two identical 99 amino acid chains. HIV protease is a member of the aspartic protease family but is structurally dissimilar to human aspartic proteases such as renin, gastricsin and cathepsin D and E, suggesting the possibility of creating inhibitors with a wide therapeutic index. At least 6 inhibitors of HIV protease are currently in clinical development: saquinavir, indinavir, ritonavir, nelfinavir (AG-1343), KNI-272 and VX-478, the first four of which have shown antiretroviral activity and acceptable tolerability in initial phase I/II clinical trials. Resistance or reduced sensitivity to the leading protease inhibitors has been reported in vivo and appears to be associated with loss of therapeutic effect. However, resistance patterns appear to be distinct. Treatment for 1 year with indinavir has been reported to lead to selection of virus in 4

patients, which was cross-resistant to all other leading protease inhibitors. On the other hand, a larger series of clinical isolates from patients receiving saquinavir alone or in combination with zidovudine for up to 3 years did not lead to virus cross-resistant to either indinavir or ritonavir. This suggests that care should be exercised in designing the sequence of protease usage. Additionally, differing resistance patterns may be used to select combinations of protease inhibitors in future trials. Data from studies combining protease inhibitors with nucleoside analogues suggest value in terms of larger and more prolonged virological and immunological marker responses than are observed with single agent therapy, and this is likely to be the primary role for protease inhibitors; both in initial combinations for patients commencing therapy and as add-in therapies for patients previously treated with antiretrovirals. However, in vitro and animal pharmacokinetic studies also give evidence of the possibility of combining protease inhibitors, potentially leading to improved bioavailability, antiviral synergy and delay in emergence of viral resistance.

L13 ANSWER 10 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 6

ACCESSION NUMBER: 96201151 EMBASE

DOCUMENT NUMBER: 1996201151

TITLE: Phorbol 12-myristate 13-acetate stimulates the release of glycosaminoglycans from cultured vascular endothelial cells: Possible involvement of protein kinase C activation.

AUTHOR: Fujii N.; Kaji T.; Yamamoto C.; Fujiwara Y.; Koizumi F.

CORPORATE SOURCE: Department of Environmental Science, Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3

SOURCE: Kanagawa-machi, Kanazawa 920-11, Japan

Thrombosis Research, (1996) 82/5 (379-387).

ISSN: 0049-3848 CODEN: THBAAA

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 018 Cardiovascular Diseases and Cardiovascular Surgery

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB We investigated the release of glycosaminoglycans (GAGs) labeled with [3H]glucosamine and [35S]sulfate into the medium from cultured bovine aortic endothelial cells stimulated by phorbol 12-myristate 13-acetate (PMA) which is an activator of protein kinase C (PKC). The GAG release was significantly accelerated by PMA without an increase in the leakage of lactate dehydrogenase but was unchanged by 4.alpha.-phorbol 12,13-didecanoate which lacks the ability of PKC activation. The acceleration of GAG release by PMA was strongly suppressed by a PKC inhibitor H-7 but not by HA 1004 which is an inactive analogue of H-7. Characterization of GAGs released into the medium revealed that PMA increased both heparan sulfate and the other GAGs in a similar degree. Although the release of GAGs stimulated by thrombin was also suppressed by another PKC inhibitor staurosporine, stimulation by plasmin was unaffected by the inhibitor. The present data suggest that protein kinase C mediates the release of endothelial cell GAGs including anticoagulant heparan sulfate and the stimulation of the release by thrombin includes this mechanism.

L13 ANSWER 11 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 7

ACCESSION NUMBER: 95256319 EMBASE

DOCUMENT NUMBER: 1995256319

TITLE: Influence of monosaccharide derivatives on liver cell glycosaminoglycan synthesis: 3-deoxy-D-xylo-hexose (3-deoxy-D-galactose) and methyl (methyl 4-chloro-4-deoxy-.beta.-D-galactopyranoside) uronate.

AUTHOR: Thomas S.S.; Plenkiewicz J.; Ison E.R.; Bols M.; Zou W.;

Szarek W.A.; Kisilevsky R.

CORPORATE SOURCE: Department of Pathology, Queen's University, Kingston, Ont.

SOURCE: K7L 3N6, Canada

Biochimica et Biophysica Acta - Molecular Basis of Disease,

(1995) 1272/1 (37-48).

ISSN: 0925-4439 CODEN: BBADEX

COUNTRY: Netherlands

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

048 Gastroenterology

037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB An improved, convenient synthesis of 3-deoxy-D-xylo-hexose (3-deoxy-D-galactose) has been developed, and the chemical synthesis of a novel monosaccharide derivative, methyl (methyl 4-chloro-4-deoxy-.beta.-D-galactopyranosid)uronate (compound 10), is described. Using primary hepatocytes in culture, each was used to explore its effect on glycosaminoglycan (GAG) synthesis. In the absence of analogues hepatocytes synthesize primarily (92-95%) heparan sulphate. At 1 mM, 3-deoxy-D-galactose had little observable effect on either liver cell GAG or protein synthesis. At 10 mM and 20 mM, 3-deoxy-D-galactose reduced [3H]glucosamine and 35S04 incorporation into hepatocyte cellular GAGs to, respectively, 75% and 60% of the control cells. This inhibition of GAG synthesis occurred without any effect on hepatocyte protein synthesis, indicating that 3-deoxy-D-galactose's effect on GAG synthesis is not mediated through an inhibition of proteoglycan core protein synthesis. Furthermore, GAGs in the presence of 20 mM of the analogue were significantly reduced in size, 17 kDa vs. 66 kDa in untreated cells. These results reflect either impaired cellular GAG chain elongation, and/or altered GAG chain degradation. Compound 10 exhibited a concentration-dependent inhibition of both hepatocyte cellular GAG and protein synthesis. At concentrations of 5, 10 and 20 mM, compound 10 inhibited GAG and protein synthesis by 20, 65 and 90%, respectively. Exogenous uridine was able to restore partially the inhibition of protein synthesis, but was unable to reverse the effect of compound 10 on GAG synthesis. These results show that part of the effect of compound 10 on GAG synthesis is not mediated by an inhibition of proteoglycan core protein synthesis. GAGs in the presence of compound 10 are half as large as those in the absence of this compound (33 and 66 kDa, respectively). These results again may reflect either impaired cellular GAG chain elongation and/or altered GAG chain degradation. Potential metabolic routes for each analogue's effect are presented.

L13 ANSWER 12 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 8

ACCESSION NUMBER: 94357878 EMBASE

DOCUMENT NUMBER: 1994357878

TITLE: Functional association of cyclophilin A with HIV-1 virions.

AUTHOR: Thali M.; Bukovsky A.; Kondo E.; Rosenwirth B.; Walsh C.T.;
Sodroski J.; Gottlinger H.G.
CORPORATE SOURCE: Division of Human Retrovirology, Dana-Farber Cancer
Institute, Harvard Medical School, Boston, MA 02115, United
States
SOURCE: Nature, (1994) 372/6504 (363-365).
ISSN: 0028-0836 CODEN: NATUAS
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Cyclophilins are a family of proteins that bind the
immunosuppressant cyclosporin A, possess peptidyl-prolyl cis-trans
isomerase activity, and assist in the folding of proteins. Human
cyclophilins A and B are host cell proteins that bind
specifically to the HIV-1 Gag polyprotein p55(gag) in
vitro. Here we report that viral particles formed by p55(gag),
in contrast to particles formed by the Gag polyproteins of other
retroviruses, contain significant amounts of cyclophilin A. Sequences in
the capsid domain of p55(gag) are both required and sufficient
for the virion-association of cyclophilin A. The association of
cyclophilin A with HIV-1 virions was inhibited in a dose-dependent manner
by cyclosporin A as well as by SDZ NIM811 ([Melle-4]cyclosporin), a
non-immunosuppressive analogue of cyclosporin A. Drug-induced
reductions in virion-associated cyclophilin A levels were accompanied by
reductions in virion infectivity, indicating that the association is
functionally relevant. Moreover, SDZ NIM811 inhibited the replication of
HIV-1 but was inactive against SIV(MAC), a primate immunodeficiency virus
closely related to HIV-1, which does not incorporate cyclophilin A.

L13 ANSWER 13 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 94362824 EMBASE
DOCUMENT NUMBER: 1994362824
TITLE: Hypoxia and cobalt stimulate lactate dehydrogenase (LDH)
activity in vascular smooth muscle cells.
AUTHOR: Marti H.H.; Jung H.H.; Pfeilschifter J.; Bauer C.
CORPORATE SOURCE: Physiologisches Institut, University Zurich-Irchel,
Winterthurerstrasse 190, CH-8057 Zurich, Switzerland
SOURCE: Pflugers Archiv European Journal of Physiology, (1994) 429/2 (216-222).
ISSN: 0031-6768 CODEN: PFLABK
COUNTRY: Germany
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 002 Physiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB O₂ plays a dominant role in the metabolism and viability of cells; changes
in O₂ supply lead to many physiological responses in the cell. Recent
reports have shown that hypoxia induces the transcription of a number of
genes, among them those for the glycolytic enzymes. We have investigated
signalling events that may lead to enhanced activity of lactate
dehydrogenase (LDH) in cultured vascular smooth muscle (VSM) cells derived
from rat aorta, grown under hypoxic conditions (1% versus 20% O₂). LDH was
chosen because this enzyme exhibits one of the largest increases in
activity among the glycolytic enzymes after hypoxic stimulation of cells.
Hypoxic exposure of VSM cells for 24 h resulted in a 2-fold increase in
LDH activity and in a 2.5-fold increase in intracellular cAMP levels.
Agents that activate adenylate cyclase, such as forskolin, cholera toxin
and 1-methyl-3-isobutylxanthine (IBMX), and thus increase cAMP production,
significantly induced LDH activity. Moreover, induction of LDH activity by
hypoxia was prevented in the presence of the protein kinase A
inhibitor N-[2-(methyl-amino)ethyl]-5-isoquinolinsulphonamide
dihydrochloride (H-8), and the cyclooxygenase inhibitor indomethacin. In
contrast to the cAMP-stimulating agents, stable cGMP analogues
[dibutyryl-cGMP, 8-bromo-cGMP], activators of protein kinase C
[12-O-tetradecanoylphorbol-13-acetate (TPA), and 1-oleoyl-2-acetyl-
glycerol (GAG)], and the calcium ionophore ionomycin did not
alter LDH activity in VSM cells kept at 20% O₂. A dose-dependent increase
in LDH activity was also observed in normoxic cells exposed to cobalt
chloride (50-200 µM), indicating that a metal binding protein
might be involved in this signalling cascade. This transition metal does
not seem to act by interfering with cellular oxidative phosphorylation,
because 10⁻⁵-10⁻⁴ M cyanide, a potent inhibitor of cell respiration, had
no effect on LDH activity, as has been also shown for the production of
erythropoietin (EPO). Thus, we suggest that the phosphorylation potential
is not crucial to the O₂-sensing mechanism regulating LDH activity and
EPO production. Our results suggest that the 'metabolic indicator' leading
to an enhanced LDH activity under hypoxic conditions in VSM cells is
represented by cAMP.

L13 ANSWER 14 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V. DUPLICATE 9

ACCESSION NUMBER: 93212454 EMBASE
DOCUMENT NUMBER: 1993212454
TITLE: A survey of synthetic HIV-1 peptides with natural and
chimeric sequences for differential reactivity with
Zimbabwean, Tanzanian and Swedish HIV-1-positive sera.
AUTHOR: Blomberg J.; Lawoko A.; Pipkorn R.; Moyo S.; Malmvall B.E.;
Shao J.; Dash R.; Tswana S.
CORPORATE SOURCE: Section of Virology, Department of Medical Microbiology,
University of Lund, Solvegaten 23, S-223 62 Lund, Sweden
SOURCE: AIDS, (1993) 7/6 (759-767).
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
017 Public Health, Social Medicine and Epidemiology
026 Immunology, Serology and Transplantation
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective: To determine whether the known sequence differences between
African and non-African HIV-1 strains are reflected in the serological
response. Design and methods: We investigated the antibody reactivity of
34 Swedish, 30 Tanzanian and 42 Zimbabwean HIV-1-positive sera to 67
synthetic peptides with sequences from North American and
African HIV-1 isolates, mostly derived from regions of gag and
env known to be antigenic. Not all sera were tested against all
peptides. Results: Differences in frequency of reactivity were
noted with peptides covering the entire third variable domain
(V3), which is a primary neutralization determinant, and the carboxyl
terminus of gp120, in two regions of gp41, and the carboxyl terminus of

p24. In env Tanzanian sera reacted preferentially with a V3 peptide from the strain JY1 (Zaire). Gradual substitutions in the central motif in V3 of ELI from GLGQ to GPGR, typical of many non-African strains, led to a gradual increase in reactivity of many Swedish sera, but did not affect Tanzanian and Zimbabwean sera, suggesting that the major epitopes recognized by these African sera are outside GPGR. V3 peptides from the MN and Z3 strains reacted with most sera, but missed 30% of those of Tanzanian origin. In the carboxyl terminus of gp120 both sets of African sera reacted preferentially with peptides from strains JY1 and MAL. Swedish sera reacted strongest with analogues from strains Z321 and HXB2. In gp41, Swedish sera showed a weak preference for reactivity with HXB2-derived peptides in the immunodominant region (amino acids 590-620), and further towards the carboxyl terminus (amino acids 620-665). Conclusion: The differences in serological reactivity were as great between Zimbabwe and Tanzania as between the two African sets and the Swedish. The geographical differences in the pattern of reactivity with HIV peptides probably depend on both host and viral variation and may be developed into a seroepidemiological tool, useful for optimization of future HIV vaccines.

L13 ANSWER 15 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 10
ACCESSION NUMBER: 94022461 EMBASE

DOCUMENT NUMBER: 1994022461

TITLE: Effects of beraprost sodium, a stable analogue of prostacyclin, on hyperplasia, hypertrophy and glycosaminoglycan synthesis of rat aortic smooth muscle cells.

AUTHOR: Koh E.; Morimoto S.; Jiang B.; Inoue T.; Nabata T.; Kitano S.; Yasuda O.; Fukuo K.; Ogiwara T.

CORPORATE SOURCE: Department of Geriatric Medicine, Osaka University Medical School, 2-2 Yamadaoka, Suita, Osaka 553, Japan

SOURCE: Artery, (1993) 20/5 (242-252).
ISSN: 0098-6127 CODEN: ARTEDR

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
018 Cardiovascular Diseases and Cardiovascular Surgery
037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The effects of beraprost sodium, a stable analogue of prostacyclin, on the syntheses of DNA, protein and glycosaminoglycans (GAG) of cultured vascular smooth muscle cells (SMC) were studied. SMC were isolated from the thoracic aorta of male Wistar rats. The syntheses of DNA, protein and GAG of SMC were determined by incorporations of [3H]thymidine, [3H]leucine and [35S]sulfuric acid, respectively. Insulin at a concentration of 10⁻⁶ M stimulated DNA synthesis 4 fold compared to control. Beraprost sodium suppressed the insulin-stimulated DNA synthesis dose-dependently at concentrations greater than 10⁻⁷ M and suppressed it by 68% at 10⁻⁵ M. Platelet derived growth factor (PDGF) at a concentration of 20 ng/ml stimulated DNA synthesis 6 fold compared to control. Beraprost sodium suppressed the PDGF-stimulated DNA synthesis dose-dependently at concentrations greater than 10⁻⁷ M and suppressed it by 51% at 10⁻⁵ M. Beraprost sodium suppressed GAG synthesis dose-dependently at concentrations greater than 10⁻⁷ M and suppressed it by 49% at 10⁻⁵ M. However, beraprost sodium at concentrations up to 10⁻⁵ M did not affect protein synthesis. These results indicate that beraprost sodium suppressed the proliferation and GAG synthesis of SMC but did not affect hypertrophy. Beraprost sodium may be a potent antiarteriosclerotic agent through suppression of hyperplasia of SMC and modification of matrix proteins.

L13 ANSWER 16 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 11

ACCESSION NUMBER: 93088179 EMBASE

DOCUMENT NUMBER: 1993088179

TITLE: Mechanism of inhibition of the retroviral protease by a Rous sarcoma virus peptide substrate representing the cleavage site between the gag p2 and p10 proteins.

AUTHOR: Cameron C.B.; Grinde B.; Jentoft J.; Leis J.; Weber I.T.; Copeland T.D.; Wlodawer A.

CORPORATE SOURCE: Dept. of Biochemistry, Case Western Reserve Univ. Med. Sch., 2119 Abington Rd., Cleveland, OH 44106-4935, United States

SOURCE: Journal of Biological Chemistry, (1992) 267/33 (23735-23741).

ISSN: 0021-9258 CODEN: JBCHA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The activity of the avian myeloblastosis virus (AMV) or the human immunodeficiency virus type 1 (HIV-1) protease on peptide substrates which represent cleavage sites found in the gag and gag-pol polyproteins of Rous sarcoma virus (RSV) and HIV-1 has been analyzed. Each protease efficiently processed cleavage site substrates found in their cognate polyprotein precursors. Additionally, in some instances heterologous activity was detected. The catalytic efficiency of the RSV protease on cognate substrates varied by as much as 30-fold. The least efficiently processed substrate, p2-p10, represents the cleavage site between the RSV p2 and p10 proteins. This peptide was inhibitory to the AMV as well as the HIV-1 and HIV-2 protease cleavage of other substrate peptides with K(i) values in the 5-20 .mu.M range. Molecular modeling of the RSV protease with the p2-p10 peptide docked in the substrate binding pocket and analysis of a series of single-amino acid-substituted p2-p10 peptide analogues suggested that this peptide is inhibitory because of the potential of a serine residue in the P1' position to interact with one of the catalytic aspartic acid residues. To open the binding pocket and allow rotational freedom for the serine in P1', there is a further requirement for either a glycine or a polar residue in P2' and/or a large amino acid residue in P3'. The amino acid residues in P1-P4 provide interactions for tight binding of the peptide in the substrate binding pocket.

L13 ANSWER 17 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 12

ACCESSION NUMBER: 92337478 EMBASE

DOCUMENT NUMBER: 1992337478

TITLE: Synthesis of stereochemically defined phosphoramidate-containing peptides: Inhibitors for the HIV-1 proteinase.

AUTHOR: Camp N.P.; Hawkins P.C.D.; Hitchcock P.B.; Gani D.

CORPORATE SOURCE: Chemistry Department, University of St. Andrews, St.

SOURCE: Andrews, Fife KY16 9ST, United Kingdom
Bioorganic and Medicinal Chemistry Letters, (1992)
1 2/9 (1047-1052).
ISSN: 0960-894X CODEN: BMCLES

COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Phosphoramidate-containing peptidic substrate analogues of the HIV-1 gag-pol proteinase-reverse transcriptase junction [-Phe-.PSI.[PO2-N]-(S)-Pro and -Phe-.PSI.[P(OMe)O-N]-(S)-Pro-], mimicks for the transition states for proteolysis, have been synthesised. The absolute stereochemistry at C-1 of the phosphonophenylalanine residue was determined by X-ray crystallography. Boc-(S)-Asn-Phe-.PSI.[PO2-N]-(S)-Pro-(S)-Ile-NH-1-Bu and Boc-(S)-Asn-(R)-Phe-.PSI.[P(OMe)O-N]-(S)-Pro-(S)-Ile-NH-1-Bu inhibit the HIV-1 proteinase.

L13 ANSWER 18 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 13
ACCESSION NUMBER: 93007882 EMBASE
DOCUMENT NUMBER: 1993007882
TITLE: Inhibition of HIV by an anti-HIV protease synthetic peptide blocks an early step of viral replication.
AUTHOR: Venaud S.; Yahi N.; Fehrentz J.L.; Guettari N.; Hirsch I.; Nisato D.; Chermann J.C.
CORPORATE SOURCE: Unite de Recherches INSERM sur, les Retrovirus et Maladies Associees, Campus de Luminy, BP 33,13273 Marseille Cedex 9, France
SOURCE: Research in Virology, (1992) 143/5 (311-319).
ISSN: 0923-2516 CODEN: RESVEY
COUNTRY: France
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English; French

AB The processing of the human immunodeficiency virus (HIV) gag and gag-pol precursor proteins by the virus-encoded protease is an essential step in maturation of infectious virus particles. Like most retroviral proteases, the HIV protease belongs to the aspartyl-protease family and can be inhibited by specific inhibitors. Twenty-four synthetic peptides known to be inhibitors of human renin were tested for inhibition of HIV replication in tissue cultures. One of them, a synthetic peptide analogue, SR41476, which has been shown to be a specific inhibitor of purified recombinant HIV1 protease in vitro, totally blocked infection with different isolates including the HIV1 LAV prototype, the highly cytopathic Zairian isolate HIV1 NDK, and HIV2 ROD, both in primary blood lymphocytes (PBL) and in the lymphoid cell lines MT4 and CEM, for at least 3 weeks. It also significantly reduced virus replication in chronically infected CEM cells, without any effect on cell proliferation. Radioimmunoprecipitation assay revealed that the inhibitor blocked processing of polyprotein precursors p55 gag and p40 gag into a mature form of gag proteins, p25 and p18. Synthetic peptide analogue SR 41476, when added before infection, efficiently inhibited formation of HIV DNA provirus and successfully suppressed synthesis of HIV-specific proteins. These results imply that the HIV protease inhibitor not only inhibited virus maturation in the late phase of the HIV replication cycle, but also interfered in the early phase, before the provirus was formed. This mechanism of antiviral activity provides new possibilities and strategies for AIDS chemotherapy.

L13 ANSWER 19 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 92124285 EMBASE
DOCUMENT NUMBER: 1992124285
TITLE: Signal transduction in glycosaminoglycan (GAG) synthesis by cultured chondrocytes and its inhibition by inflammatory cell-derived hydrogen peroxide.
AUTHOR: Matsubara T.; Kimura T.; Kuroda T.; Hirohata K.
CORPORATE SOURCE: Department of Orthopaedic Surg, Kobe University School of Medi, 7 Chome Kusunoki-cho, Chuo-ku, Kobe, Japan
SOURCE: British Journal of Rheumatology, (1992) 31/4 SUPPL. (27-32).
ISSN: 0263-7103 CODEN: BJRHDP
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Conference Article
FILE SEGMENT: 005 General Pathology and Pathological Anatomy
031 Arthritis and Rheumatism
037 Drug Literature Index

LANGUAGE: English
SUMMARY LANGUAGE: English

AB Signal transduction in glycosaminoglycan (GAG) synthesis by chondrocytes has been studied. The activity of various subspecies of protein kinase C (PKC) in chondrocytes derived from rodent costal cartilage and bovine articular cartilage has been determined and the role of PKC in GAG synthesis as well as the possible interactions of PKC with calcium- or cyclic AMP (cAMP)-dependent systems in the synthesis of GAG. To investigate GAG synthesis in inflammatory conditions, the effects of hydrogen peroxide on PKC activity of the chondrocytes and PKC-mediate GAG synthesis have been studied. 12-O-tetradecanoylphorbol-13-acetate (TPA), an activator of PKC, increased GAG synthesis in a dose-dependent fashion. This suggests that PKC up-regulates the synthesis of GAG in cultured chondrocytes. This increase was not significantly affected by simultaneous addition of the calcium ionophore, ionomycin, or dibutyryl cAMP (db-cAMP), a cAMP analogue. Ionomycin and db-cAMP, when used alone, did not significantly alter GAG synthesis by chondrocytes. Thus there appears to be no interaction between PKC and calcium- or cAMP-mediated systems in GAG synthesis. The increase in GAG synthesis induced by TPA was significantly ($P < 0.01$) reduced by simultaneous addition of hydrogen peroxide (10^{-6} M), without affecting cell viability. The activity of PKC in chondrocytes pretreated with 10^{-6} M hydrogen peroxide was also significantly inhibited. Thus hydrogen peroxide which is generated by inflammatory cells may be important in suppression of GAG synthesis in inflammatory conditions.

L13 ANSWER 20 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.
ACCESSION NUMBER: 91321861 EMBASE
DOCUMENT NUMBER: 1991321861
TITLE: Purification and biochemical characterization of

recombinant simian immunodeficiency virus protease and comparison to human immunodeficiency virus type 1 protease.
 AUTHOR: Grant S.K.; Deckman I.C.; Minnich M.D.; Culp J.; Franklin S.; Dreyer G.B.; Tomaszek Jr. T.A.; Debouck C.; Meek T.D.
 CORPORATE SOURCE: Dept. of Medicinal Chemistry, SmithKline Beecham, Pharmaceuticals, 709 Swedeland Road, King of Prussia, PA 19406, United States
 SOURCE: Biochemistry, (1991) 30/34 (8424-8434).
 ISSN: 0006-2960 CODEN: BICHAW
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB Simian immunodeficiency virus protease (SIV-PR) was produced in *Escherichia coli* with a recombinant expression system in which the mature enzyme autoprocessed from a precursor form. Recombinant SIV and HIV-1 (human immunodeficiency virus, type 1) proteases were purified from bacterial cell lysates by use of sequential steps of ammonium sulfate precipitation and size-exclusion and ion-exchange chromatography. The amino acid composition, amino-terminal sequence, and molecular weight (monomer) of the recombinant SIV-PR were in accord with that of the 99 amino acid polypeptide predicted from the SIV(Mac)-PR nucleotide sequence. The active form of SIV-PR was shown to be dimeric by gel filtration chromatography. Inhibition by pepstatin A, time-dependent inactivation by 1,2-epoxy-3-(4-nitrophenoxy)propane, and pH rate profiles using oligopeptide substrates demonstrated that SIV-PR behaves as an aspartic protease. Recombinant HIV-1 Pr55(gag) precursor was processed in vitro by SIV-PR and HIV-1 PR with indistinguishable proteolytic patterns upon NaDodSO₄-polyacrylamide gel electrophoresis. Oligopeptide substrates for HIV-1 PR were found to be suitable substrates for recombinant SIV-PR with the exception of a peptide containing the site identified for p66/p51 cleavage (Phe-Tyr) within HIV-1 reverse transcriptase (RT). Several synthetic peptide analogues inhibitors of HIV-1 PR were also potent inhibitors of SIV-PR, indicating that SIV infection in macaques and rhesus monkeys should be useful models for the preclinical evaluation of acquired immunodeficiency syndrome (AIDS) therapeutics targeted toward the virally encoded HIV-1 protease.

L13 ANSWER 21 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 14
 ACCESSION NUMBER: 91284073 EMBASE
 DOCUMENT NUMBER: 1991284073
 TITLE: Evidence for a 'Cysteine-Histidine box' metal-binding site in an *Escherichia coli* aminoacyl-tRNA synthetase.
 AUTHOR: Miller W.T.; Hill K.A.W.; Schimmel P.
 CORPORATE SOURCE: Dept. of Biology, Massachusetts Inst. of Technol., Cambridge, MA 02139, United States
 SOURCE: Biochemistry, (1991) 30/28 (6970-6976).
 ISSN: 0006-2960 CODEN: BICHAW
 COUNTRY: United States
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 004 Microbiology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB *Escherichia coli* alanyl-tRNA synthetase contains the sequence Cys-X2-Cys-X6-His-X2-His. This motif is distinct from the zinc fingers of DNA-binding proteins but has some similarity to the Cys-X2-Cys-X4-His-X4-Cys zinc-binding motif of retroviral gag proteins, where it has a role in RNA packaging. In Ala-tRNA synthetase, this sequence is located in an amino-terminal domain which has the site for docking the acceptor end of the tRNA near the bound aminoacyl adenylate and is immediately adjacent in the sequence to the location of a mutation that affects the specificity of tRNA recognition. We show here that Ala-tRNA synthetase contains approximately 1 mol of zinc/mol of polypeptide and that addition of the zinc chelator 1,10-phenanthroline inhibits its aminoacylation activity. Conservative mutations of specific cysteine or histidine residues in the 'Cys-His box' destabilize and inactivate the enzyme, whereas mutations of intervening amino acids do not inactivate. The possibility that this motif can bind zinc (or cobalt) was demonstrated with a synthetic 22 amino acid peptide that is based on the sequence of the alanine enzyme. The peptide-cobalt complex has the spectral characteristics of tetrahedral coordination geometry. The results establish that the Cys-His box motif of Ala-tRNA synthetase has the potential to form a specific complex with zinc (at least in the context of a synthetic peptide analogue) and suggest that this motif is important for enzyme stability/activity.

L13 ANSWER 22 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 15
 ACCESSION NUMBER: 91185841 EMBASE
 DOCUMENT NUMBER: 1991185841
 TITLE: Antibodies to gp41 and nef in otherwise HIV-negative homosexual man with Kaposi's sarcoma.
 AUTHOR: Bowden F.J.; McPhee D.A.; Deacon N.J.; Cumming S.A.; Doherty R.R.; Sonza S.; Lucas C.R.; Crowe S.M.
 CORPORATE SOURCE: Macfarlane Burnet Centre, Medical Research, Yarra Bend Road, Fairfield, Vic. 3078, Australia
 SOURCE: Lancet, (1991) 337/8753 (1313-1314).
 ISSN: 0140-6736 CODEN: LANCAO
 COUNTRY: United Kingdom
 DOCUMENT TYPE: Journal; Article
 FILE SEGMENT: 013 Dermatology and Venereology
 LANGUAGE: English
 SUMMARY LANGUAGE: English

AB A homosexual man with histologically confirmed Kaposi's sarcoma remained seronegative for HIV-1, HIV-2, and HTLV-1 on conventional tests over a 4-year period. HIV cultures were also negative on thirteen separate occasions. However, serum antibodies to synthetic peptide analogues of the gp41 and nef regions of HIV-1 were consistently detected on an enzyme immunoassay. Tests with the polymerase chain reaction with primers directed to the gag and env regions were negative. The antigens to which the antibodies were produced might have come from a defective HIV mutant, another retrovirus, or a hitherto unknown 'agent of Kaposi's sarcoma' with similar antigenic epitopes.

L13 ANSWER 23 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 16
 ACCESSION NUMBER: 92066148 EMBASE
 DOCUMENT NUMBER: 1992066148
 TITLE: Investigation of the role of metalloproteinases in recombinant human interleukin-1 β -induced degradation of rat femoral head cartilage.
 AUTHOR: Seed M.P.; Thomson T.A.; Gardner C.R.
 CORPORATE SOURCE: Dep of Experimental Pathology, William Harvey Research Inst., St Bartholomews Hosp Med Coll, Charter House

SOURCE: Square, London EC1M 6BQ, United Kingdom
 Drugs under Experimental and Clinical Research, (1991) 17/7 (355-361).
 ISSN: 0378-6501 CODEN: DECRDP

COUNTRY: Switzerland

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 005 General Pathology and Pathological Anatomy
 029 Clinical Biochemistry
 030 Pharmacology
 031 Arthritis and Rheumatism
 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The mechanism of proteoglycan (GAG) loss from rat femoral articular cartilage (FRC) induced by recombinant human interleukin-1.β. (rhIL-1.β.) in vitro has been investigated. The metalloproteinase inhibitor 1,10-phenanthroline, the serine proteinase inhibitor N.α-p-tosyl-L-lysine chloromethyl ketone (TLCK), the activator of latent metalloproteinase p-aminophenylmercuric acid (APMA), and an inhibitory metalloproteinase substrate analogue U27391 were tested for their ability to modulate rhIL-1.β. induced GAG loss and GAG synthesis ([35S]O4 uptake) inhibition. As expected 1,10-phenanthroline inhibited GAG loss, however [35S]O4 incorporation was significantly reduced. TLCK was without effect, and APMA inhibited both parameters. U27391 reversed both the inhibition of [35S]O4 incorporation and GAG loss. It is concluded that the adverse effects on proteoglycan metabolism explain the inhibitory actions of 1,10-phenanthroline and APMA, whilst the action of TLCK may indicate that serine proteinases are not involved in the activation of latent metalloproteinase. U27391 exhibited chondroprotective activity and confirmed the induction of either metalloproteinases such as stromelysin or collagenase by rhIL-1.β.

L13 ANSWER 24 OF 41 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1992:45773 BIOSIS

DOCUMENT NUMBER: BA93:25748

TITLE: ANALYSIS OF NON-INFECTIOUS HIV PARTICLES PRODUCED IN PRESENCE OF HIV PROTEINASE INHIBITOR.

AUTHOR(S): SCHAETZEL H; GELDERBLUM T R; NITSCHKO H; VON DER HELM K

CORPORATE SOURCE: MAX-VON-PETTENKOFER-INSTITUT, UNIVERSITAET MUENCHEN, PETTENKOFER-STRASSE 9A, D-W-8000 MUNICH 2, GERMANY.

SOURCE: ARCH VIROL, (1991) 120 (1-2), 71-82.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB Newly developed substrate analogue peptidomimetics are able to inhibit the human immunodeficiency virus, HIV-1 proteinase at nanomolar concentration. In HIV infected cell culture they exhibit antiviral activity. We have analyzed the non-infectious HIV particles produced in chronically HIV infected cell culture in presence of one of these inhibitors. The total production of virus particles was not substantially reduced in drug treated cultures, compared to non-inhibited control cultures, but the infectivity of these virus particles was reduced about 100 fold. The processing of gag and gag-pol protein precursor was inhibited; only borderline activity of reverse transcriptase (RT) could be detected in these particles and they contained nonprocessed gag precursor protein. Thin section electron microscopy of inhibitor-treated, HIV-infected cells revealed reduced viral cytopathogenicity and both inhibition of particle assembly and incomplete maturation of the particles formed. The HIV particles produced in the presence of the proteinase inhibitor were studded with envelope glycoprotein knobs and often comprised multiple budding regions, but were morphologically immature.

L13 ANSWER 25 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 17

ACCESSION NUMBER: 91049671 EMBASE

DOCUMENT NUMBER: 1991049671

TITLE: Reconstitution of constitutive secretion using semi-intact cells: Regulation by GTP but not calcium.

AUTHOR: Miller S.G.; Moore H.-P.H.

CORPORATE SOURCE: Division of Cell and Developmental Biology, Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, United States

SOURCE: Journal of Cell Biology, (1991) 112/1 (39-54).

ISSN: 0021-9525 CODEN: JCLBA3

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 037 Drug Literature Index

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Regulated exocytosis in many permeabilized cells can be triggered by calcium and nonhydrolyzable GTP analogues. Here we examine the role of these effectors in exocytosis of constitutive vesicles using a system that reconstitutes transport between the trans-Golgi region and the plasma membrane. Transport is assayed by two independent methods: the movement of a transmembrane glycoprotein (vesicular stomatitis virus glycoprotein [VSV G protein]) to the cell surface; and the release of a soluble marker, sulfated glycosaminoglycan (GAG) chains, that have been synthesized and radiolabeled in the trans-Golgi. The plasma membrane of CHO cells was selectively perforated with the bacterial cytolysin streptolysin-O. These perforated cells allow exchange of ions and cytosolic proteins but retain intracellular organelles and transport vesicles. Incubation of the semi-intact cells with ATP and a cytosolic fraction results in transport of VSV G protein and GAG chains to the cell surface. The transport reaction is temperature dependent, requires hydrolyzable ATP, and is inhibited by N-ethylmaleimide. Non-hydrolyzable GTP analogs such as GTP.γS, which stimulate the fusion of regulated secretory granules, completely abolish constitutive secretion. The rate and extent of constitutive transport between the trans-Golgi and the plasma membrane is independent of free Ca²⁺ concentrations. This is in marked contrast to fusion of regulated secretory granules with the plasma membrane, and transport between the ER and the cis-Golgi.

L13 ANSWER 26 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 18

ACCESSION NUMBER: 91331428 EMBASE

DOCUMENT NUMBER: 1991331428

TITLE: HIV-1 proteinase is required for synthesis of pro-viral DNA.

AUTHOR: Baboonian C.; Dalgleish A.; Bountiff L.; Gross J.; Oroszlan S.; Rickett G.; Smith-Burchnell C.; Troke P.; Merson J.

CORPORATE SOURCE: Pfizer Central Research, Sandwich, Kent, CT11 9NJ, United Kingdom

SOURCE: Biochemical and Biophysical Research Communications, (1991) 179/1 (17-24).
ISSN: 0006-291X CODEN: BBRCA
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HIV-1 proteinase activity is thought to occur primarily post-integration by cleaving the viral Gag and Gag-Pol polyproteins. Its role in the pre-integration stages of viral replication, however, has not been studied in detail. Here we report that a synthetic peptide analogue, UK-88,947, which is a specific inhibitor of purified HIV-1 proteinase, inhibits the processing of the viral polyproteins in cultures of HIV-1 infected cells and prevents the formation of mature, infectious virions. Analysis of DNA from HIV-1 infected cells treated with UK-88,947 showed that viral DNA synthesis was inhibited when the compound was added to cultures one hour before infection. Similar results were obtained when AZT was used. Neither HIV-1 reverse transcriptase or the replication of FIV are inhibited by UK-88,947.

L13 ANSWER 27 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 90259916 EMBASE
DOCUMENT NUMBER: 1990259916
TITLE: Evidence for involvement of the protein kinase C pathway in the activation of p37(v-mos) protein kinase.
AUTHOR: Al-Bagdadi P.; Singh B.; Arlinghaus R.B.
CORPORATE SOURCE: Dept. of Molecular Pathology, University of Texas, M.D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030, United States
SOURCE: Oncogene, (1990) 5/8 (1251-1257).
ISSN: 0950-9232 CODEN: ONCNE5
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 015 Cancer
029 Clinical Biochemistry
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Protein kinases are known to undergo phosphorylation to regulate their activity. To determine whether the protein kinase activity of p37(v-mos) was similarly regulated, we investigated the influence of two well known protein kinases, namely protein kinase C and protein kinase A, on the activity of p37(v-mos) in vivo. NIH3T3 cells chronically transformed with Moloney murine sarcoma virus 124 were treated with high concentrations (200-400 nM) of phorbol 12-myristate 13-acetate (PMA) for 24-48 h, concentrations known to result in the total loss of protein kinase C by causing its translocation from the cytosol to cell membranes where it is downregulated. PMA treatment caused a drastic decrease in the protein kinase activity of p37(v-mos) without affecting its steady state level. Similar results were obtained with p85(gag-mos) expressed in ts110 Mo-MuSV transformed NRK cells. Control treatment with an inactive analogue of PMA, 4- α -phorbol 12,13-didecanoate, had no effect on the p37(v-mos) protein kinase activity. Treatment of cells with a direct chemical inhibitor of protein kinase C, H-7 (1-(5-isoquinoline sulfonyl)-2-methylpiperazine dihydrochloride), approximately halved p37(v-mos) kinase activity, although the drug did not inhibit p37(v-mos) kinase activity directly in vitro. In contrast to the PMA effect, in vivo activation of protein kinase A by 8-(4-chlorophenylthio)-adenosine 3',5' cyclic monophosphate did not affect p37(v-mos) protein kinase activity levels. These findings indicate that the protein kinase C pathway but not the protein kinase A pathway modulates v-mos protein kinase activity.

L13 ANSWER 28 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 19

ACCESSION NUMBER: 90348024 EMBASE
DOCUMENT NUMBER: 1990348024
TITLE: An HIV-1 and HIV-2 cross-reactive cytotoxic T-cell epitope.
AUTHOR: Nixon D.P.; Huet S.; Rothbard J.; Kieny M.-P.; Delchambre M.; Thiriart C.; Rizza C.R.; Gotch F.M.; McMichael A.J.
CORPORATE SOURCE: Molecular Immunology Group, Inst. of Molecular Medicine, John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom
SOURCE: AIDS, (1990) 4/9 (841-845).
ISSN: 0269-9370 CODEN: AIDSET
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 026 Immunology, Serology and Transplantation
047 Virology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The HLA-B27-restricted HIV gag cytotoxic T-lymphocyte (CTL) epitope, 265-279, is highly conserved amongst HIV-1 isolates, only one, HIV-1(ELI), having a single amino acid substitution. Over the same region HIV-2 differs by five amino acids. As a broadly cross-protective AIDS vaccine should protect against infection from all isolates of HIV-1 and HIV-2, we tested CTL specific for the HIV-1 265-279 epitope with peptide analogues from HIV-1(ELI), HIV-2 and two simian immunodeficiency virus (SIV) isolates, and with recombinant vaccinia viruses expressing the respective gag genes, to determine whether there was any cross-reactivity for this CTL epitope. CTL from the HIV-1-infected donor could recognize the HIV-1(ELI) peptide, the HIV-2 peptide and recombinant vaccinia virus-infected target and one of the two SIV peptide-treated targets. Epitopes that exhibit such cross-activity may be valuable in vaccine design.

L13 ANSWER 29 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 20

ACCESSION NUMBER: 90034078 EMBASE
DOCUMENT NUMBER: 1990034078
TITLE: Substrate analogue inhibition and active site titration of purified recombinant HIV-1 protease.
AUTHOR: Tomasselli A.G.; Olsen M.K.; Hui J.O.; Staples D.J.; Sawyer T.K.; Heinrikson R.L.; Tomich C.-S.C.
CORPORATE SOURCE: Biopolymer Chemistry Res. Unit, The Upjohn Company, Kalamazoo, MI 49001, United States
SOURCE: Biochemistry, (1990) 29/1 (264-269).
ISSN: 0006-2960 CODEN: BICHAW
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 047 Virology
LANGUAGE: English

SUMMARY LANGUAGE: English

AB The aspartyl protease of human immunodeficiency virus 1 (HIV-1) has been expressed in *Escherichia coli* at high levels, resulting in the formation of inclusion bodies which contain denatured insoluble aggregates of the protease. After solubilization of these inclusion bodies in guanidinium chloride, the protease was purified to apparent homogeneity by a single-step reverse-phase HPLC procedure. The purified, but inactive, protein was denatured in 8 M urea and refolded to produce the active protease. Enzyme activity was demonstrated against the substrate H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH, modeled after the cleavage region between residues 128 and 135 in the HIV gag polyprotein. With this substrate, a V_{\max} of $1.3 \pm 0.2 \mu\text{mol}/(\text{min} \cdot \text{mg})$ and K_M of $2.0 \pm 0.3 \text{ nM}$ were determined at pH 5.5. Pepstatin (Iva-Val-Val-Sta-Ala-Sta-OH) and substrate analogues with the Tyr-Pro residues substituted by Sta, by Phe-PSI-(CH₂N)Pro, and by Leu-PSI-(CH(OH)CH₂)Val inhibited the protease with K_I values of 360 nM, 3690 nM, 3520 nM, and <10 nM, respectively. All were competitive inhibitors, and the tightest binding compound provided an active site titrant for the quantitative determination of enzymatically active HIV-1 protease.

L13 ANSWER 30 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 90036706 EMBASE

DOCUMENT NUMBER: 1990036706

TITLE: Inhibition of HIV-1 protease in infected T-lymphocytes by synthetic peptide analogues.

AUTHOR: Meek T.D.; Lambert D.M.; Dreyer G.B.; Carr T.J.; Tomaszek Jr. T.A.; Moore M.L.; Strickler J.E.; Debouck C.; Hyland L.J.; Matthews T.J.; Metcalf B.W.; Petteway S.R.

CORPORATE SOURCE: Department of Medicinal Chemistry, Smith Kline and French Laboratories, 709 Swedeland Road, King of Prussia, PA 19406, United States

SOURCE: Nature, (1990) 343/6253 (90-92).

ISSN: 0028-0836 CODEN: NATUAS

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 047 Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The gag and pol genes of the human immunodeficiency virus type 1 (HIV-1) are translated as two polyproteins, Pr55(gag) and Pr160(gag-pol), which are subsequently cleaved by the action of a virus-encoded protease into the four structural gag proteins of the virion core (p17, p24, p7 and p6) and the pol-encoded enzymes essential for retrovirus replication (protease, reverse transcriptase, ribonuclease H, and endonuclease). Mutational inactivation of the proteases of HIV-1 and other retroviruses results in immature, non-infectious virions, indicating that exogenous inhibition of the protease may represent an attractive approach to anti-AIDS therapy. Here we demonstrate that synthetic peptide analogues, which are potent inhibitors of purified HIV-1 protease, inhibit the processing of the viral polyproteins in cultures of HIV-1-infected T lymphocytes and attenuate viral infectivity.

L13 ANSWER 31 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 90031055 EMBASE

DOCUMENT NUMBER: 1990031055

TITLE: Inhibition of human immunodeficiency virus 1 protease in vitro: Rational design of substrate analogue inhibitors.

AUTHOR: Dreyer G.B.; Metcalf B.W.; Tomaszek Jr. T.A.; Carr T.J.; Chandler III A.C.; Hyland L.; Fakhoury S.A.; Magaard V.W.; Moore M.L.; Strickler J.E.; Debouck C.; Meek T.D.

CORPORATE SOURCE: Dept. of Medicinal Chemistry, SKF Laboratories, P.O. Box 1539, King of Prussia, PA 19406-0939, United States

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1989) 86/24 (9752-9756).

ISSN: 0027-8424 CODEN: PNASA6

COUNTRY: United States

DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 047 Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Inhibitors of the protease from human immunodeficiency virus 1 (HIV-1) were designed, synthesized, and kinetically characterized. Analogues of a heptapeptide substrate of HIV-1 protease with sequence similar to the p17-p24 cleavage site in the natural substrate, Pr55(gag), were synthesized in which the scissile dipeptide bond was replaced with bonds from six categories of stable mimics of an aspartic proteolysis transition state or intermediate. These mimics included an analogue of statine, hydroxyethylene isosteres, two categories of phosphinic acids, a reduced amide isostere, and an .alpha., .alpha.-difluoroketone. The resulting peptide analogues were linear competitive inhibitors of purified recombinant HIV-1 protease with inhibition constants ranging from 18 nM to 40 .mu.M depending on the type of inhibitor. A truncated inhibitor, an analogue of a hexapeptide, retained full inhibitory potency. The most potent inhibitors, containing the hydroxyethylene isostere, effectively blocked the proteolytic processing of a recombinant form of Pr55(gag) by HIV-1 protease in a cell-free assay.

L13 ANSWER 32 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V. DUPLICATE 21

ACCESSION NUMBER: 88209084 EMBASE

DOCUMENT NUMBER: 1988209084

TITLE: Adenallene and cytallene: Acyclic nucleoside analogues that inhibit replication and cytopathic effect of human immunodeficiency virus in vitro.

AUTHOR: Hayashi S.; Phadtare S.; Zemlicka J.; Matsukura M.; Mitsuya H.; Broder S.

CORPORATE SOURCE: The Clinical Oncology Program, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, United States

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1988) 85/16 (6127-6131)

ISSN: 0027-8424 CODEN: PNASA6

COUNTRY: United States

DOCUMENT TYPE: Journal

FILE SEGMENT: 029 Clinical Biochemistry

047 Virology

037 Drug Literature Index

030 Pharmacology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Although several antiretroviral compounds are already known, almost no acyclic nucleoside derivatives lacking an oxacyclopentane have been reported to exert significant inhibition against human immunodeficiency virus type 1 (HIV-1) in vitro. We found two unsaturated acyclic nucleoside derivatives, adenallene [9-(4'-hydroxy-1',2'-butadienyl)adenine] and cytallene [1-(4'-hydroxy-1',2'-butadienyl)cytosine], that protect various CD4+ T-cell lines from the infectivity and cytopathic effect of HIV-1. These compounds inhibit the expression of HIV-1 gag-encoded protein and suppress viral DNA synthesis at concentrations that do not affect functions of normal T cells in vitro. They also inhibit the in vitro infectivity of another human retrovirus, HIV-2. Further in vitro analyses of the anti-HIV-1 activity revealed that the presence of two cumulated double bonds between the 1' and 2' carbons and between the 2' and 3' carbons confers antiretroviral activity in certain pyrimidine or purine derivatives containing a four-carbon chain. We have also found that the 4'-hydroxyl group is critical for the in vitro anti-HIV activity of adenallene. Our observations may provide structure-activity relationships for acyclic nucleoside analogues and may be of value in developing a new class of experimental drugs for the therapy of HIV-related diseases.

L13 ANSWER 33 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 88067901 EMBASE

DOCUMENT NUMBER: 1988067901

TITLE: N-myristoylation of p60(src). Identification of a myristoyl-CoA:glycylpeptide N-myristoyltransferase in rat tissues.

AUTHOR: Glover C.J.; Goddard C.; Felsted R.L.

CORPORATE SOURCE: Laboratory of Biological Chemistry, Division of Cancer Treatment, Developmental Therapeutics Program, National Cancer Institute, Bethesda, MD 20892, United States

SOURCE: Biochemical Journal, (1988) 250/2 (485-491).

ISSN: 0264-6021 CODEN: BIJOAK

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal

FILE SEGMENT: 029 Clinical Biochemistry

LANGUAGE: English

SUMMARY LANGUAGE: English

AB A 16-residue synthetic peptide corresponding to the N-terminal sequence of p60(src) was used as the acyl acceptor in an assay for myristoyl-CoA:glycylpeptide N-myristoyltransferase in rat tissues. An additional C-terminal tyrosine amide was added to this peptide to facilitate radioiodination and enhance detectability. Reverse-phase h.p.l.c. enabled the simultaneous detection and quantification of the peptide substrate and its N-myristoylated product. N-Myristoyltransferase activity was highest in the brain with decreasing activities in lung, small intestine, kidney, heart, skeletal muscle and liver. Brain activity was distributed approximately equally between the 100 000 g pellet and supernatant fractions. The soluble enzyme exhibited a K(m) (app.) of 20 .mu.M for the src peptide and an optimum between pH 7.0 and 7.5. Maximum N-acylating activity was seen with myristoyl (C(14:0))-CoA with lower activities found with the C(10:0)-CoA and C(12:0)-CoA homologues. No activity was obtained with palmitoyl (C(18:0))-CoA but this derivative inhibited N-myristoyltransferase activity > 50% at equimolar concentrations with myristoyl-CoA. With a decapeptide corresponding to the N-terminal sequence of the cyclic AMP-dependent protein kinase catalytic subunit as the acyl acceptor, the brain enzyme displayed a K(m) (app.) of 117 .mu.M and was about 14-fold less catalytically effective than with the p60(src) acyl acceptor. Transferase activity was also seen with a 16-residue peptide corresponding to the N-terminal sequence of the HIV p17(gag) structural protein. Inhibition studies with shorter src peptide analogues indicated an enzyme specificity for the p60(src) acyl acceptor beyond 9 residues.

L13 ANSWER 34 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 89042837 EMBASE

DOCUMENT NUMBER: 1989042837

TITLE: Molecular biology of HIV.

AUTHOR: Peterlin B.M.; Luciw P.A.

CORPORATE SOURCE: Howard Hughes Medical Institute, University of California, San Francisco, CA 94143, United States

SOURCE: AIDS, (1988) 2/SUPPL. 1 (S29-S40).

ISSN: 0269-9370 CODEN: AIDSET

COUNTRY: United Kingdom

DOCUMENT TYPE: Journal

FILE SEGMENT: 026 Immunology, Serology and Transplantation

029 Clinical Biochemistry

047 Virology

LANGUAGE: English

SUMMARY LANGUAGE: English

AB Much has been learned about HIV in the past 5 years. Sequencing of the viral genes was followed by the expression and characterizations of their protein products in prokaryotic and eukaryotic systems. Now, great efforts are being made to crystallize HIV proteins and examine their structures. This will allow for design and synthesis of chemical analogues that might interfere with the actions of HIV enzymes and trans-activators, block viral morphogenesis and budding, or prevent interactions between virions and cellular membranes. HIV has been isolated in many countries, from many individuals and from the same individual over time, and from different tissues in patients with distinct symptoms. These viral isolates will elucidate interactions between host immunity and HIV, determinants of viral tropism, and subtleties in the regulation of HIV gene expression. Closer examination of tat and rev might solve fundamental conundrums in retrovirology dealing with differences in the rates of initiation of transcription between the LTRs of the provirus and with the regulation of processing and splicing of viral transcripts. Cell biology of signaling, receptor mediated endocytosis and cell fusion will benefit from studies of naf, and of the interactions between env products, CD4 and other host receptors. Some of the above processes will be found responsible for HIV-induced cytopathology and cell death. As a consequence of these investigations, we hope that a chink in the armour of HIV will be found leading to therapeutics that will block the virus and ameliorate the symptoms or cure AIDS.

L13 ANSWER 35 OF 41 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1987:418282 BIOSIS

DOCUMENT NUMBER: BA84:84944

TITLE: PHARMACOLOGICAL INHIBITION OF IN-VITRO INFECTIVITY OF HUMAN T LYMPHOTROPIC VIRUS TYPE 1.

AUTHOR(S): MATSUSHITA S; MITSUYA H; REITZ M S; BRODER S

CORPORATE SOURCE: CLINICAL ONCOLOGY PROGRAM, BUILD. 10, ROOM 13N238, NATL.

SOURCE: CANCER INST., BETHESDA, MD. 20892.
J CLIN INVEST. (1987) 80 (2), 394-400.
CODEN: JCINAO. ISSN: 0021-9738.

FILE SEGMENT: BA; OLD
LANGUAGE: English

AB Human T lymphocytic virus type I (HTLV-I) is an exogenous RNA tumor virus etiologically linked to adult T cell leukemia and related diseases. In this paper, we describe that two 2',3'-dideoxynucleoside analogues, erythro 3'-azido-2',3'-dideoxy-thymidine (also called azidothymidine) and 2',3'-dideoxycytidine can inhibit the infectivity of HTLV-I against helper/inducer T cells in vitro. Both 2',3'-dideoxynucleoside analogues inhibited the overgrowth of target T cells, which was a consequence of virally mediated transformation, when they were exposed to the virus and cultured with the compounds. A profound decrease in the expression of HTLV-I gag-proteins was also observed. Moreover, we observed that the amount of proviral DNA detected in cellular DNA from the target T cells was substantially reduced when the cells were protected by the compounds against the virus and that at certain concentrations of the compounds the synthesis of viral DNA was completely suppressed. These results may be of value in developing a new pharmacological strategy for preventing the replication and possibly blocking the transmission of HTLV-I and related retroviruses in human beings.

L13 ANSWER 36 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 22

ACCESSION NUMBER: 86104838 EMBASE
DOCUMENT NUMBER: 1986104838

TITLE: Comparative inhibitory effects of suramin and other selected compounds on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy-associated virus (LAV).

AUTHOR: Balzarini J.; Mitsuya H.; De Clercq E.; Broder S.
CORPORATE SOURCE: Rega Institute for Medical Research, University of Leuven, B-3000 Leuven, Belgium
SOURCE: International Journal of Cancer, (1986) 37/3 (451-457).

COUNTRY: United States
DOCUMENT TYPE: Journal

FILE SEGMENT: 037 Drug Literature Index
016 Cancer
025 Hematology
047 Virology
030 Pharmacology
026 Immunology, Serology and Transplantation

LANGUAGE: English

AB Suramin and various other selected compounds were evaluated for their in vitro inhibitory effects on the infectivity and replication of human T-cell lymphotropic virus (HTLV-III)/lymphadenopathy-associated virus (LAV). As parameters for infectivity and replication, respectively, we followed the cytopathic effect of HTLV-III/LAV on ATH 8 cells, a T-cell clone with high susceptibility to HTLV-III/LAV, and the expression of HTLV-III/LAV p24 gag protein in H9 cells infected with HTLV-III/LAV. As the most effective inhibitors of HTLV-III/LAV the following substances emerged (in order of decreasing activity): Evans Blue, suramin > phosphonoformic acid > Direct Yellow 50. Several purine nucleoside analogues including vidarabine, tubercidin, neplanocin A, dihydroxypropyladenine, pyrazofurin and ribavirin were not inhibitory to HTLV-III/LAV. In our test systems, involving a high multiplicity of infection, HPA-23, previously reported to be effective against LAV reverse transcriptase, showed no inhibitory effect on HTLV-III/LAV infectivity for ATH 8 cells and proved only weakly inhibitory to HTLV-III/LAV replication in H9 cells. Thus, among the anionic dyes that are structurally related to suramin, compounds were found which were as active as suramin itself, if not more so.

L13 ANSWER 37 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 86196219 EMBASE
DOCUMENT NUMBER: 1986196219

TITLE: Antibodies to the ATP-binding site of the human epidermal growth factor (EGF) receptor as specific inhibitors of EGF-stimulated protein-tyrosine kinase activity.

AUTHOR: Gullick W.J.; Downward J.; Foulkes J.G.; Waterfield M.D.
CORPORATE SOURCE: Protein Chemistry Laboratory, Imperial Cancer Research Fund Laboratories, London WC2A 3PX, United Kingdom
SOURCE: European Journal of Biochemistry, (1986) 158/2 (245-253).

COUNTRY: Germany
DOCUMENT TYPE: Journal

FILE SEGMENT: 029 Clinical Biochemistry
030 Pharmacology

LANGUAGE: English

AB A region of the primary amino acid sequence of the epidermal growth factor receptor (EGF) protein-tyrosine kinase, which is involved in ATP binding, was identified using chemical modification and immunological techniques. EGF receptor was ¹⁴C-labelled with the ATP analogue 5'-p-fluorosulphonylbenzoyladenine and from a tryptic digest a single radiolabelled peptide was isolated. The amino acid sequence was determined to be residues 716-724 and hence lysine residue 721 is located within the ATP-binding site. Antisera were elicited in rabbits to a synthetic peptide identical to residues 716-727 of the EGF receptor and the homologous sequence in v-erb B transforming protein from avian erythroblastosis virus. The affinity-purified antibodies precipitated human EGF receptor from A431 cells and placenta, and the v-erb B protein from erythroblasts. The antibodies inhibited EGF-stimulated receptor protein-tyrosine kinase autophosphorylation and phosphorylation of an exogenous peptide substrate containing tyrosine. The antibodies did not immunoprecipitate the transforming proteins pp60(v-src) or P120(gag-abl) or cAMP-dependent protein kinase, proteins which have homologous but not identical sequences surrounding the lysine residue within the ATP-binding site, nor did they react with the platelet-derived growth factor receptor. The antibodies had no effect on the kinase activity of purified v-abl protein in solution. The antibodies may therefore be a specific inhibitor of the tyrosine kinase of the EGF receptor.

L13 ANSWER 38 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.DUPLICATE 23

ACCESSION NUMBER: 86063760 EMBASE
DOCUMENT NUMBER: 1986063760

TITLE: 3'-Azido-3'-deoxythymidine (BW A509U): An antiviral agent that inhibits the infectivity and cytopathic effect of

human T-lymphotropic virus type III/lymphadenopathy-associated virus in vitro.
 Mitsuya H.; Weinhold K.J.; Purman P.A.; et al.
 CORPORATE SOURCE: The Clinical Oncology Program, National Cancer Institute, Bethesda, MD 20205, United States
 SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1985) 82/20 (7096-7100).
 CODEN: PNASAG
 COUNTRY: United States
 DOCUMENT TYPE: Journal
 FILE SEGMENT: 037 Drug Literature Index
 047 Virology
 049 Forensic Science Abstracts
 026 Immunology, Serology and Transplantation
 016 Cancer

LANGUAGE: English

AB The acquired immune deficiency syndrome (AIDS) is thought to result from infection of T cells by a pathogenic human retrovirus, human T-lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV). In this report, we describe the antiviral effects of a thymidine analogue, 3'-azido-3'-deoxythymidine (BW A509U), which, as a triphosphate, inhibits the reverse transcriptase of HTLV-III/LAV. This agent blocks the expression of the p24 gag protein of HTLV-III/LAV in H9 cells following exposure to virus. The drug also inhibits the cytopathic effect of HTLV-III(B) (a virus derived from a pool of American patients) and HTLV-III/RF-II (an isolate obtained from a Haitian patient that differs by about 20% in the amino acid sequence of the envelope gene from several isolates of HTLV-III/LAV, including HTLV-III(B), analyzed so far). 3'-Azido-3'-deoxythymidine also completely blocks viral replication as assessed by reverse transcriptase production in normal human peripheral blood mononuclear cells exposed to HTLV-III(B). Finally, at concentrations of 3'-azido-3'-deoxythymidine that blocks the in vitro infectivity and cytopathic effect of HTLV-III(B), the in vitro immune functions of normal T cells remain basically intact.

L13 ANSWER 39 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 78313217 EMBASE
 DOCUMENT NUMBER: 1978313217
 TITLE: Cell-free synthesis of a precursor polyprotein containing both gag and pol gene products by Rauscher murine leukemia virus 35S RNA.
 AUTHOR: Murphy Jr. E.C.; Kopchick J.J.; Watson K.F.; Arlinghaus R.B.
 CORPORATE SOURCE: Dept. Biol., Univ. Texas Syst. Cancer Cent., M.D. Anderson Hosp. Tum. Inst., Houston, Tex 77030, United States
 SOURCE: Cell, (1978) 13/2 (359-369).
 CODEN: CELLB5
 COUNTRY: United States
 DOCUMENT TYPE: Journal
 FILE SEGMENT: 016 Cancer
 025 Hematology
 047 Virology
 022 Human Genetics

LANGUAGE: English

AB Translation of Rauscher murine leukemia virus 35S RNA in mRNA-dependent m-RNA-dependent protein-synthesizing system results in the synthesis of polypeptides with apparent molecular weights of 200,000, 75,000 and 65,000 daltons. Each of these polypeptides was immunoprecipitable with anti-p30 serum, while only the 200,000 dalton size class was specifically recognized by antiserum prepared against purified reverse transcriptase. Intracellular Pr200(gag-pol) has been shown to contain p30 tryptic peptide sequences (Arcement et al., 1976) and to share antigenic determinants with the gag proteins p30, p15, p12 and p10 and the reverse transcriptase (Jamjoom, Naso and Arlinghaus, 1977). These results and others (Jamjoom et al., 1977) led the authors to the conclusion that Pr200(gag-pol) is the initial translation product that leads to the formation of mature reverse transcriptase. In the present study, 9 of 11 methionine-containing tryptic peptides found in an anti-reverse transcriptase-precipitable 80,000 dalton molecular weight virion polypeptide (p80(pol)) were contained in Pr200(gag-pol). In addition, virion p80(pol) co-migrates in SDS-polyacrylamide gels with the major polypeptide found in partially purified preparations of active reverse transcriptase. The in vitro synthesized 200,000 dalton polypeptide was identical to intracellular Pr200(gag-pol) as determined by comparing ion-exchange profiles of methionine-labeled tryptic peptides. The frequency of synthesis of the in vitro synthesized Pr200(gag-pol) was 1/25 to 1/20 that of the combined synthesis of the 65,000 and 75,000 dalton gag precursors. A similar ratio of Pr200(gag-pol) to Pr65(gag) and Pr80(gag) has been observed in viral infected cells. Thus 35S viral genomic RNA is an mRNA for both gag and pol gene products. Experiments with the arginine analogue canavanine suggest that the usual termination signal occurs after the translation of Pr80(gag). The authors propose that the Pr200(gag-pol) results from an occasional read-through (5% frequency) of a single termination codon at the end of the gag gene.

L13 ANSWER 40 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 78361411 EMBASE
 DOCUMENT NUMBER: 1978361411
 TITLE: Cell-free synthesis of Rauscher murine leukemia virus 'gag' and 'gag-pol' precursor polyproteins from virion 35 S RNA in a mRNA dependent translation system derived from mouse tissue culture cells.
 AUTHOR: Murphy Jr. E.C.; Arlinghaus R.B.
 CORPORATE SOURCE: Dept. Biol., Univ. Texas Syst. Cancer Cent., M.D. Anderson Hosp. Tum. Inst., Houston, Tex. 77030, United States
 SOURCE: Virology, (1978) 86/2 (329-343).
 CODEN: VIRLAX
 COUNTRY: United States
 DOCUMENT TYPE: Journal
 FILE SEGMENT: 016 Cancer
 047 Virology

LANGUAGE: English

AB Using a mRNA-dependent cell-free protein synthesis system derived from mouse tissue culture cell extracts by treatment with micrococcal nuclease, we have examined the capacity of 35S genomic RNA from Rauscher leukemia virus (RLV) to code for the synthesis of viral proteins. Analysis of the polypeptide product by SDS-polyacrylamide gel electrophoresis (SDS-PAGE) indicated that RLV 35S RNA directed the synthesis of RLV-specific polypeptides of 55,000, 65,000,

75,000, and 200,000 apparent molecular weights, identical in size to the known intracellular precursors of the RLV mature polypeptides. None of the individual mature virus proteins appeared to be synthesized. If canavanine, an arginine analogue, was substituted for arginine under conditions for cell-free protein synthesis, a RLV-specific polypeptide with a molecular weight of approximately 80,000 was synthesized at the expense of the 65,000 and 75,000 MW polypeptides. Monospecific antisera directed against p30, p15, p12, and p10 recognized the 65,000, 75,000, 80,000 and 200,000 MW polypeptides, indicating that each shared antigenic determinants with all of these 'gag' proteins. Using the appropriate authentic RLV precursor polypeptides as standards, comparative tryptic maps were performed with the [3H]tyrosine or [35S]methionine-labeled in vitro-synthesized 65,000 and 200,000 MW polypeptides. The 65,000 MW polypeptide was found to be identical to Pr65(gag), a 65,000 MW RLV gag protein precursor obtained from infected cells by immunoprecipitation and gel electrophoresis. The 200,000 MW in vitro-synthesized polypeptide was found to contain methionine-labeled tryptic peptides characteristic of the RLV reverse transcriptase ('pol') and p30.

L13 ANSWER 41 OF 41 EMBASE COPYRIGHT 2002 ELSEVIER SCI. B.V.

ACCESSION NUMBER: 78103275 EMBASE
DOCUMENT NUMBER: 1978103275
TITLE: Evolutionary relationships between gag gene-coded proteins of murine and primate endogenous type C RNA viruses.
AUTHOR: Barbacid M.; Stephenson J.R.; Aaronson S.A.
CORPORATE SOURCE: Lab. RNA Tum. Viruses, Nat. Cancer Inst., Bethesda, Md. 20014, United States
SOURCE: Cell. (1977) 10/4 (641-648).
CODEN: CELLE5
COUNTRY: United States
DOCUMENT TYPE: Journal
FILE SEGMENT: 047 Virology
016 Cancer
022 Human Genetics
029 Clinical Biochemistry
LANGUAGE: English

AB Several low molecular weight proteins of endogenous type C viruses of the RD114/baboon group are compared with the gag gene translational products of endogenous type C viruses of murine origin. The p10 proteins of each virus group are shown to be immunologically and biochemically related, while the p12 proteins of RD114/baboon viruses are demonstrated to share antigenic determinants with murine viral p15. Moreover, highly type-specific phosphoproteins, p15 of RD114/baboon viruses and p12 of murine viruses, are shown to possess very similar biochemical properties. These findings, along with previous studies indicating immunologic cross-reactivity between their major internal antigens, p30, demonstrate that each of the gag gene-coded proteins of murine type C viruses has an analogue in viruses of the RD114/baboon group. The immunologic and biochemical relatedness of their gag gene translational products supports the concept of a common progenitor in the evolution of these endogenous viruses.

=> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002

L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3
L5 0 S L1 AND L3
L6 4675 S L3 AND HIV
L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
L8 184 S L7 (P) AIDS
L9 801 S L7 (P) (HIV OR NEF OR AIDS)
L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
L11 110 S L7 (P) (NEF OR GAG)
L12 64 S L11 AND PD<19980507
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)

=> s 17 (P) (HIV or AIDS)
L14 800 L7 (P) (HIV OR AIDS)

=> s 114 not nucleo?
L15 575 L14 NOT NUCLEO?

=> s 115 and PD<19980507
'19980507' NOT A VALID FIELD CODE
3 FILES SEARCHED...
L16 262 L15 AND PD<19980507

=> s 116 not 113
L17 244 L16 NOT L13

=> dup rem 117
PROCESSING COMPLETED FOR L17
L18 155 DUP REM L17 (89 DUPLICATES REMOVED)

=> s 118 and (NEF or GAG)
L19 15 L18 AND (NEF OR GAG)

=> dis 119 1-15 ibib abs

L19 ANSWER 1 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1998:258358 BIOSIS
DOCUMENT NUMBER: PREV199800258358
TITLE: Serological detection of attenuated HIV-1 variants with nef gene deletions.
AUTHOR(S): Greenway, Alison L.; Mills, John; Rhodes, David; Deacon, Nicholas J.; McPhee, Dale A. (1)
CORPORATE SOURCE: (1) ACBU, Natl. Cent. HIV Virol. Res., Macfarlane Burnet Cent. Med. Res., P.O. Box 254, Fairfield, VIC 3078 Australia
SOURCE: AIDS (London), (April 16, 1998) Vol. 12, No. 6, pp. 555-561.
ISSN: 0269-9370.
DOCUMENT TYPE: Article
LANGUAGE: English

AB Objective: To investigate whether members of a transfusion-linked cohort (the Sydney Bloodbank Cohort) infected with a nef-deleted strain of HIV-1 could be differentiated from individuals infected with wild-type strains of HIV-1 by characterizing the Nef antibody response of cohort members. Design: Retrospective and prospective analysis of the nef gene sequence and the antibody response to Nef peptides in HIV-infected subjects. Methods: Plasma was obtained from all individuals of the Sydney cohort, and from a variety of HIV-1-infected and uninfected controls. Antibodies recognizing full-length recombinant HIV-1NL43 Nef protein and synthetic peptide analogues were assessed by enzyme-linked immunosorbent assay. Results: All 34 individuals infected with wild-type HIV-1 had antibodies reacting with full-length Nef protein as well as with a series of synthetic peptides (6-23-mers) spanning most of the Nef protein of HIV-1NL43. Although the HIV-1 quasispecies infecting the Sydney cohort had a consensus deletion of the nef gene corresponding to amino-acids 165-206, HIV-1 strains from individual members of the cohort had additional deletions comprising up to 80% of the nef gene. Members of the cohort had antibodies to peptides homologous to all regions of the Nef protein tested, except for a single peptide (amino-acids 162-177) that lies within the consensus nef deletion for the cohort quasispecies. Conclusion: These data show that nef-deleted strains of HIV-1 can be detected serologically. In the Sydney cohort, detection of antibodies to all regions of Nef tested, except that corresponding to amino-acids 162-177, suggests that observed deletions outside this domain occurred after this virus had infected these subjects and stimulated an immune response. A Nef peptide serological assay may be useful for identifying further examples of individuals infected with nef-deleted, attenuated HIV-1 quasispecies and for assessing the evolution of those variants in vivo.

L19 ANSWER 2 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:489083 BIOSIS

DOCUMENT NUMBER: PREV199799788286

TITLE: Transfer of the HIV-1 cyclophilin-binding site to simian immunodeficiency virus from Macaca mulatta can confer both cyclosporin sensitivity and cyclosporin dependence.

AUTHOR(S): Bukovsky, Anatoly A.; Weimann, Andreas; Accola, Molly A.; Gottlinger, Heinrich G.

CORPORATE SOURCE: Div. Human Retrovirology, Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA 02115 USA

SOURCE: Proceedings of the National Academy of Sciences of the United States of America, (1997) Vol. 94, No. 20, pp. 10943-10948.

ISSN: 0027-8424.

DOCUMENT TYPE: Article

LANGUAGE: English

AB HIV-1 specifically incorporates the peptidyl prolyl isomerase cyclophilin A (CyPA), the cytosolic receptor for the immunosuppressant cyclosporin A (CsA). HIV-1 replication is inhibited by CsA as well as by nonimmunosuppressive CsA analogues that bind to CyPA and interfere with its virion association. In contrast, the related simian immunodeficiency virus SIV-mac, which does not interact with CyPA, is resistant to these compounds. The incorporation of CyPA into HIV-1 virions is mediated by a specific interaction between the active site of the enzyme and the capsid (CA) domain of the HIV-1 Gag polyprotein. We report here that the transfer of HIV-1 CA residues 86-93, which form part of an exposed loop, to the corresponding position in SIV-mac resulted in the efficient incorporation of CyPA and conferred an HIV-1-like sensitivity to a nonimmunosuppressive cyclosporin. HIV-1 CA residues 86-90 were also sufficient to transfer the ability to efficiently incorporate CyPA, provided that the length of the CyPA-binding loop was preserved. However, the resulting SIV-mac mutant required the presence of cyclosporin for efficient virus replication. The results indicate that the presence or absence of a type II tight turn adjacent to the primary CyPA-binding site determines whether CyPA incorporation enhances or inhibits viral replication. By demonstrating that CyPA-binding-site residues can induce cyclosporin sensitivity in a heterologous context, this study provides direct in vivo evidence that the exposed loop between helices IV and V of HIV-1 CA not merely constitutes a docking site for CyPA but is a functional target of this cellular protein.

L19 ANSWER 3 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1997:251687 BIOSIS

DOCUMENT NUMBER: PREV199799550890

TITLE: The non-immunosuppressive cyclosporin A analogue SDZ NIM 811 inhibits cyclophilin A incorporation into virions and virus replication in human immunodeficiency virus type 1-infected primary and growth-arrested T cells.

AUTHOR(S): Mlynar, Edith (1); Bevec, Dorian; Billich, Andreas; Rosenwirth, Brigitte; Steinkasserer, Alexander (1)

CORPORATE SOURCE: (1) Sandoz Res. Inst., Brunnerstr. 59, A-1235 Vienna Austria

SOURCE: Journal of General Virology, (1997) Vol. 78, No. 4, pp. 825-835.

ISSN: 0022-1317.

DOCUMENT TYPE: Article

LANGUAGE: English

AB SDZ NIM 811 is a cyclosporin A (CsA) analogue that is completely devoid of immunosuppressive capacity but exhibits potent and selective antihuman immunodeficiency virus type 1 (HIV-1) activity. Binding to cyclophilin A, the intracellular receptor for cyclosporins, is a prerequisite for HIV-1 inhibition by cyclosporins. Cyclophilin A was demonstrated to bind to HIV-1 p24-gag and this cyclophilin-Gag interaction leads to the incorporation of cyclophilin A into HIV-1 virions. SDZ NIM 811 inhibits this protein interaction, and this is likely to be the molecular basis for its antiviral activity. Here, we show that in activated primary T cells SDZ NIM 811 interferes with two stages of the virus replication cycle: (i) translocation of pre-integration complexes into the nucleus and (ii) production of infectious virus particles. SDZ NIM 811 not only inhibits translocation of HIV-1 pre-integration complexes in primary T cells, but also in a growth-arrested T cell line. In vivo, most T lymphocytes are quiescent, but serve nevertheless as a major and inducible HIV-1 reservoir in infected individuals. Significant amounts of cyclophilin A were found to be associated with virus particles propagated in primary T cells. SDZ NIM 811 caused a strong reduction in the amount of incorporated cyclophilin A, thereby reducing infectivity.

Thus, cyclophilin A seems to be necessary for HIV-1 replication in primary T cells.

L19 ANSWER 4 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1995:43866 BIOSIS

DOCUMENT NUMBER: PREV199598058166

TITLE: Functional association of cyclophilin A with HIV-1 virions.

AUTHOR(S): Thali, Markus (1); Bukovsky, Anatoly; Kondo, Eisaku; Rosenwirth, Brigitte; Walsh, Christopher T.; Sodroski, Joseph; Gottlinger, Heinrich G.

CORPORATE SOURCE: (1) Inst. Microbiol., University Lausanne, CH-1066

SOURCE: Epalinges Switzerland
Nature (London), (1994) Vol. 372, No. 6504, pp. 363-365.
ISSN: 0028-0836.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Cyclophilins are a family of proteins that bind the immunosuppressant cyclosporin A, possess peptidyl-prolyl cis-trans isomerase activity, and assist in the folding of proteins. Human cyclophilins A and B are host cell proteins that bind specifically to the HIV-1 Gag polyprotein p55-gag in vitro. Here we report that viral particles formed by p55-gag, in contrast to particles formed by the Gag polyproteins of other retroviruses, contain significant amounts of cyclophilin A. Sequences in the capsid domain of p55-gag are both required and sufficient for the virion-associated of cyclophilin A. The association of cyclophilin A with HIV-1 virions was inhibited in a dose-dependent manner by cyclosporin A as well as by SDZ NIM811 ((Melle-4)cyclosporin), a non-immunosuppressive analogue of cyclosporin A. Drug induced reductions in virion-associated cyclophilin A levels were accompanied by reductions in virion infectivity, indicating that the association is functionally relevant. Moreover, SDZ NIM811 inhibited the replication of HIV-1 but was inactive against SIV-MAC, a primate immunodeficiency virus closely related to HIV-1, which does not incorporate cyclophilin A.

L19 ANSWER 5 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:415321 BIOSIS

DOCUMENT NUMBER: PREV199396081046

TITLE: A survey of synthetic HIV-1 peptides with natural and chimeric sequences for differential reactivity with

AUTHOR(S): Zimbabwean, Tanzanian and Swedish HIV-1-positive sera. Blomberg, Jonas (1); Lawoko, Alex; Pipkorn, Ruediger; Moyo, Sylvester; Malmvall, Bo Erik; Shao, John; Dash,

CORPORATE SOURCE: Rabinarayan, Tswana, Sam
(1) Section Virol., Dep. Med. Microbiol., Univ. Lund,

SOURCE: Solvegatan 23d, S-223 62 Lund Sweden
AIDS (Philadelphia), (1993) Vol. 7, No. 6, pp. 759-767.
ISSN: 0269-9370.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Objective: To determine whether the known sequence differences between African and non-African HIV-1 strains are reflected in the serological response. Design and methods: We investigated the antibody reactivity of 34 Swedish, 30 Tanzanian and 42 Zimbabwean HIV-1-positive sera to 67 synthetic peptides with sequences from North American and African HIV-1 isolates, mostly derived from regions of gag and env known to be antigenic. Not all sera were tested against all peptides. Results: Differences in frequency of reactivity were noted with peptides covering the entire third variable domain (V3), which is a primary neutralization determinant, and the carboxyl terminus of gp120, in two regions of gp41, and the carboxyl terminus of p24. In env Tanzanian sera reacted preferentially with a V3 peptide from the strain JY1 (Zaire). Gradual substitutions in the central motif in V3 of ELI from GLGQ to GPGR, typical of many non-African strains, led to a gradual increase in reactivity of many Swedish sera, but did not affect Tanzanian and Zimbabwean sera, suggesting that the major epitopes recognized by these African sera are outside GPGR. V3 peptides from the MN and Z3 strains reacted with most sera, but missed 30% of those of Tanzanian origin. In the carboxy terminus of gp120 both sets of African sera reacted preferentially with peptides from strains JY1 and MAL. Swedish sera reacted strongest with analogues from strains Z321 and HXB2. In gp41, Swedish sera showed a weak preference for reactivity with HXB2-derived peptides in the immunodominant region (amino acids 590-620), and further towards the carboxyl terminus (amino acids 620-665). Conclusion: The differences in serological reactivity were as great between Zimbabwe and Tanzania as between the two African sets and the Swedish. The geographical differences in the pattern of reactivity with HIV peptides probably depend on both host and viral variation and may be developed into a seroepidemiological tool, useful for optimization of future HIV vaccines.

L19 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:138235 BIOSIS

DOCUMENT NUMBER: PREV199395071035

TITLE: Inhibition of HIV by an anti-HIV protease synthetic peptide blocks an early step of viral replication.

AUTHOR(S): Venaud, S.; Yahi, N.; Fehrentz, J. L.; Guettari, N.; Nisato, D.; Hirsch, I.; Chermann, J. C. (1)

CORPORATE SOURCE: (1) Unite Recherches INSERM Retrovirus Maladies Associees,

SOURCE: Campus Luminy, BP 33, 13273 Marseille Cedex 9 France
Research in Virology, (1992) Vol. 143, No. 5, pp. 311-319.

ISSN: 0923-2516.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English; French

AB The processing of the human immunodeficiency virus (HIV) gag and gag-pol precursor proteins by the virus-encoded protease is an essential step in maturation of infectious virus particles. Like most retroviral proteases, the HIV protease belongs to the aspartyl-protease family and can be inhibited by specific inhibitors. Twenty-four synthetic peptides known to be inhibitors of human renin were tested for inhibition of HIV replication in tissue cultures. One of them, a synthetic peptide analogue, SR 41476, which has been shown to be a specific inhibitor of purified recombinant HIV1 protease in vitro, totally blocked infection with different isolates including the HIV1 LAV prototype, the highly cytopathic Zairian isolate HIV1 NDK, and HIV2 ROD, both in primary blood lymphocytes (PBL) and in the lymphoid cell lines MT4 and CEM, for at least 3 weeks. It also significantly reduced virus replication in chronically infected CEM cells, without any effect on cell proliferation. Radioimmunoassay revealed that the inhibitor blocked

processing of polyprotein precursors p55 gag and p40 gag into a mature form of gag proteins, p25 and p18. Synthetic peptide analogue SR 41476, when added before infection, efficiently inhibited formation of HIV DNA provirus and successfully suppressed synthesis of HIV-specific proteins. These results imply that the HIV protease inhibitor not only inhibited virus maturation in the late phase of the HIV replication cycle, but also interfered in the early phase, before the provirus was formed. This mechanism of antiviral activity provides new possibilities and strategies for AIDS chemotherapy.

L19 ANSWER 7 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:73668 BIOSIS

DOCUMENT NUMBER: PREV199395038168

TITLE: Mechanism of inhibition of the retroviral protease by a Rous sarcoma virus peptide substrate representing the cleavage site between the gag p2 and p10 proteins.

AUTHOR(S): Cameron, Craig E.; Grinde, Bjorn; Jentoft, Joyce; Leis, Jonathan (1); Weber, Irene T.; Copeland, Terry D.; Wlodawer, Alexander

CORPORATE SOURCE: (1) Dep. Biochem., Case Western Reserve Univ. Sch. Med., 2119 Abington Rd., Cleveland, Ohio 44106-4935

SOURCE: Journal of Biological Chemistry, (1992) Vol. 267, No. 33, pp. 23735-23741. ISSN: 0021-9258.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The activity of the avian myeloblastosis virus (AMV) or the human immunodeficiency virus type 1 (HIV-1) protease on peptide substrates which represent cleavage sites found in the gag and gag-pol polyproteins of Rous sarcoma virus (RSV) and HIV-1 has been analyzed. Each protease efficiently processed cleavage site substrates found in their cognate polyprotein precursors. Additionally, in some instances heterologous activity was detected. The catalytic efficiency of the RSV protease on cognate substrates varied by as much as 30-fold. The least efficiently processed substrate, p2-p10, represents the cleavage site between the RSV p2 and p10 proteins. This peptide was inhibitory to the AMV as well as the HIV-1 and HIV-2 protease cleavage of other substrate peptides with K-i values in the 5-20 mM range. Molecular modeling of the RSV protease with the p2-p10 peptide docked in the substrate binding pocket and analysis of a series of single-amino acid-substituted p2-p10 peptide analogues suggested that this peptide is inhibitory because of the potential of a serine residue in the P1' position to interact with one of the catalytic aspartic acid residues. To open the binding pocket and allow rotational freedom for the serine in P1', there is a further requirement for either a glycine or a polar residue in P2' and/or a large amino acid residue in P3'. The amino acid residues in P1-P4 provide interactions for tight binding of the peptide in the substrate binding pocket.

L19 ANSWER 8 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1993:48802 BIOSIS

DOCUMENT NUMBER: PREV199395025104

TITLE: Synthesis of stereochemically defined phosphonamidate-containing peptides: Inhibitors for the HIV-1 proteinase. Camp, Nicholas P.; Hawkins, Paul C. D. (1); Hitchcock, Peter B.; Gani, David (1)

CORPORATE SOURCE: (1) Chem. Dep., Purdie Building, University, St. Andrews, Fife KY16 9ST UK

SOURCE: Bioorganic & Medicinal Chemistry Letters, (1992) Vol. 2, No. 9, pp. 1047-1052. ISSN: 0960-894X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Phosphonamidate-containing peptidic substrate analogues of the HIV-1 gag-pol proteinase-reverse transcriptase junction)-Phe-PSI(PO-2-N)-(S)-Pro- and -Phe-PSI(P(OMe)O-N)-(S)-Pro-(, mimicks for the transition states for proteolysis, have been synthesised. The absolute stereochemistry at C-1 of the phosphonophenylalanine residue was determined by X-ray crystallography. Boc-(S)-Asn-Phe-PSI(PO-2-N)-(S)-Pro-(S)-Pro-(S)-Ile-NH-i-Bu and Boc-(S)-Asn-(R)-Phe-PSI(P(OMe)O-N)-(S)-Pro-(S)-Ile-NH-i-Bu inhibit the HIV-1 proteinase.

L19 ANSWER 9 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1991:479825 BIOSIS

DOCUMENT NUMBER: BA92:113585

TITLE: HIV-1 PROTEINASE IS REQUIRED FOR SYNTHESIS OF PRO-VIRAL DNA.

AUTHOR(S): BABOONIAN C; DALGLEISH A; BOUNTIFF L; GROSS J; OROSZLAN S; RICKETT G; SMITH-BURNELL C; TROKE P; MERSON J

CORPORATE SOURCE: PFIZER CENT. RES., SANDWICH, KENT, CT13 9NJ, ENGL.

SOURCE: BIOCHEM BIOPHYS RES COMMUN, (1991) 179 (1), 17-24. CODEN: BBRCA9. ISSN: 0006-291X.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB HIV-1 proteinase activity is thought to occur primarily post-integration by cleaving the viral gag and Gag-Pol polyproteins. Its role in the pre-integration stages of viral replication, however, has not been studied in detail. Here we report that a synthetic peptide analogue, UK-88,947, which is a specific inhibitor of purified HIV-1 proteinase, inhibits the processing of the viral polyproteins in cultures of HIV-1 infected cells and prevents the formation of mature, infectious virions. Analysis of DNA from HIV-1 infected cells treated with UK-88,947 showed that viral DNA synthesis was inhibited when the compound was added to cultures one hour before infection. Similar results were obtained when AZT was used. Neither HIV-1 reverse transcriptase or the replication of PIV are inhibited by UK-88,947.

L19 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1991:343477 BIOSIS

DOCUMENT NUMBER: BA92:42852

TITLE: ANTIBODIES TO GP41 AND NKF IN OTHERWISE

HIV-NEGATIVE HOMOSEXUAL MAN WITH KAPOSI'S SARCOMA.

AUTHOR(S): BOWDEN F J; MCPHEE D A; DEACON N J; CUMMING S A; DOHERTY R; SONZA S; LUCAS C R; CROWE S M

CORPORATE SOURCE: MACFARLEN BURNET CENTRE MED. RES., YARRA BEND ROAD, FAIRFIELD, VICTORIA 3078, AUST.

SOURCE: LANCET (N AM ED), (1991) 337 (8753), 1313-1314. CODEN: LANAAI.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB A homosexual man with histologically confirmed Kaposi's sarcoma remained seronegative for HIV-1, HIV-2, and HTLV-1 on conventional tests over a 4-year period. HIV cultures were also negative on thirteen separate occasions. However, serum antibodies to synthetic peptide analogues of the gp41 and nef regions of HIV-1 were consistently detected on an enzyme immunoassay. Tests with the polymerase chain reaction with primers directed to the gag and env regions were negative. The antigens to which the antibodies were produced might have come from a defective HIV mutant, another retrovirus, or a hitherto unknown "agent of Kaposi's sarcoma" with similar antigenic epitopes.

L19 ANSWER 11 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1991:71484 BIOSIS

DOCUMENT NUMBER: BA91:40144

TITLE: AN HIV-1 AND HIV-2 CROSS-REACTIVE CYTOTOXIC T-CELL EPITOPE.

AUTHOR(S): NIXON D F; HUET S; ROTHBARD J; KIENV M-P; DELCHAMBRE M;

THIRIART C; RIZZA C R; GOTCH F M; MCMICHAEL A J

CORPORATE SOURCE: MOLECULAR IMMUNOL. GROUP, INST. MOLECULAR MED., JOHN

RADCLIFFE HOSP., HEADINGTON, OXFORD OX3 9DU, UK.

SOURCE: AIDS (PHILA), (1990) 4 (9), 841-846.

CODEN: AIDSET. ISSN: 0269-9370.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The HLA-B27-restricted HIV gag cytotoxic T-lymphocyte (CTL) epitope, 265-279, is highly conserved amongst HIV-1 isolates, only one, HIV-1ELI, having a single amino acid substitution. Over the same region HIV-2 differs by five amino acids. As a broadly cross-protective AIDS vaccine should protect against infection from all isolates of HIV-1 and HIV-2, we tested CTL specific for the HIV-1 265-279 epitope with peptide analogues from HIV-1ELI, HIV-2 and two simian immunodeficiency virus (SIV) isolates, and with recombinant vaccinia viruses expressing the respective gag genes, to determine whether there was any cross-reactivity for this CTL epitope. CTL from the HIV-1-infected donor could recognize the HIV-1ELI peptide, the HIV-2 peptide and recombinant vaccinia virus-infected target and one of the two SIV peptide-treated targets. Epitopes that exhibit such cross-reactivity may be valuable in vaccine design.

L19 ANSWER 12 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1990:140327 BIOSIS

DOCUMENT NUMBER: BR38:61777

TITLE: INHIBITION OF HIV-1 PROTEASE IN INFECTED

T-LYMPHOCYTES BY SYNTHETIC PEPTIDE

ANALOGUES.

AUTHOR(S): MEER T D; LAMBERT D M; DREYER G B; CARR T J; TOMASZEK T A

JR; MOORE M L; STRICKLER J E; DEBOUCK C; HYLAND L J; ET AL

CORPORATE SOURCE: DEP. MED. CHEM., SMITH KLINE AND FRENCH LAB., 709 SWEDENLAND

RD., KING PRUSSIA, PA. 19406, USA.

SOURCE: Nature (London), (1990) 343 (6253), 90-92.

CODEN: NATUAS. ISSN: 0028-0836.

FILE SEGMENT: BR; OLD

LANGUAGE: English

L19 ANSWER 13 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1990:116285 BIOSIS

DOCUMENT NUMBER: BA89:65776

TITLE: SUBSTRATE ANALOGUE INHIBITION AND ACTIVE SITE TITRATION OF

PURIFIED RECOMBINANT HIV-1 PROTEASE.

AUTHOR(S): TOMASELLI A G; OLSEN M K; HUI J O; STAPLES D J; SAWYER T

K; HEINRIKSON R L; TOMICH C-S C

CORPORATE SOURCE: BIOPOLYMER CHEM. RES. UNIT, UPJOHN CO., KALAMAZOO, MICH.

49001.

SOURCE: BIOCHEMISTRY, (1990) 29 (1), 264-269.

CODEN: BICHAW. ISSN: 0006-2960.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB The aspartyl protease of human immunodeficiency virus 1 (HIV-1) has been expressed in Escherichia coli at high levels, resulting in the formation of inclusion bodies which contain denatured insoluble aggregates of the protease. After solubilization of these inclusion bodies in guanidinium chloride, the protease was purified to apparent homogeneity by a single-step reverse-phase HPLC procedure. The purified, but inactive, protein was denatured in 8 M urea and refolded to produce the active protease. Enzyme activity was demonstrated against the substrate H-Val-Ser-Gln-Asn-Tyr-Pro-Ile-Val-OH, modeled after the cleavage region between residues 128 and 135 in the HIV gag polypeptide. With this substrate, a V_{max} of 1.3 \pm 0.2 μ mol/(min \cdot mg) and K_M of 2.0 \pm 0.3 mM were determined at pH 5.5. Pepstatin (Iva-Val-Val-Sta-Ala-Sta-OH) and substrate analogues with the Tyr-Pro residues substituted by Sta, by Phe .PSI.[CH2N]Pro, and by Leu.PSI.[CH(OH)CH2]Val inhibited the protease with K_I values of 360 nM, 3690 nM, 3520 nM, and $<$ 10 nM, respectively. All were competitive inhibitors, and the tightest binding compound provided an active site titrant for the quantitative determination of enzymatically active HIV-1 protease.

L19 ANSWER 14 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1990:86711 BIOSIS

DOCUMENT NUMBER: BA89:46062

TITLE: INHIBITION OF HUMAN IMMUNODEFICIENCY VIRUS 1 PROTEASE

IN-VITRO RATIONAL DESIGN OF SUBSTRATE ANALOGUE INHIBITORS.

AUTHOR(S): DREYER G B; METCALP B W; TOMASZEK T A JR; CARR T J;

CHANDLER A C III; HYLAND L; FAKHOURY S A; MAGAARD V W;

MOORE M L; ET AL

CORPORATE SOURCE: DEP. PEPTIDE CHEM., SMITH KLINE AND FRENCH LAB., P.O. BOX

1539, KING OF PRUSSIA, PA. 19406-0939.

SOURCE: PROC NATL ACAD SCI U S A, (1989) 86 (24), 9752-9756.

CODEN: PNASA6. ISSN: 0027-8424.

FILE SEGMENT: BA; OLD

LANGUAGE: English

AB Inhibitors of the protease from human immunodeficiency virus 1 (HIV-1) were designed, synthesized, and kinetically characterized. Analogues of a heptapeptide substrate of HIV-1 protease with sequence similar to the p17-p24 cleavage site in the natural substrate, Pr55gag, were synthesized in which the scissile dipeptide bond was replaced with bonds from six categories of stable mimics of an aspartic proteolysis transition state or intermediate. These mimics included an analogue of statine, hydroxyethylene isosteres, two categories of phosphinic acids, a reduced amide isostere, and an

.alpha.,.alpha.-difluoroketone. The resulting peptide analogues were linear competitive inhibitors of purified recombinant HIV-1 protease with inhibition constants ranging from 18 nM to 40 .mu.M depending on the type of inhibitor. A truncated inhibitor, an analogue of a hexapeptide, retained full inhibitory potency. The most potent inhibitors, containing the hydroxyethylene isostere, effectively blocked the proteolytic processing of a recombinant form of Pr55gag by HIV-1 protease in a cell-free assay.

L19 ANSWER 15 OF 15 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.

ACCESSION NUMBER: 1986:120637 BIOSIS
DOCUMENT NUMBER: BA81:31053
TITLE: 3'-AZIDO-3'-DEOXYTHYMIDINE BW-A-509U AN ANTIVIRAL AGENT THAT INHIBITS THE INFECTIVITY AND CYTOPATHIC EFFECT OF HUMAN T LYMPHOTROPIC VIRUS TYPE III-LYMPHADENOPATHY-ASSOCIATED VIRUS IN-VITRO.
AUTHOR(S): MITSUYA H; WEINHOLD K J; FURMAN P A; ST CLAIR M H; LEHRMAN S N; GALLO R C; BOLOGNESI D; BARRY D W; BRODER S
CORPORATE SOURCE: CLINICAL ONCOLOGY PROGRAM, NATIONAL CANCER INST., BETHESDA, MD 20205.
SOURCE: PROC NATL ACAD SCI U S A, (1985) 82 (20), 7096-7100.
CODEN: PNASA6. ISSN: 0027-8424.
FILE SEGMENT: BA; OLD
LANGUAGE: English

AB The acquired immune deficiency syndrome (AIDS) is thought to result from infection of T cells by a pathogenic human retrovirus, human T-lymphotropic virus type III (HTLV-III) or lymphadenopathy-associated virus (LAV). In this report, we describe the antiviral effects of a thymidine analogue, 3'-azido-3'-deoxythymidine (BW A509U), which, as a triphosphate, inhibits the reverse transcriptase of HTLV-III/LAV. This agent blocks the expression of the p24 gag protein of HTLV-III/LAV in H9 cells following exposure to virus. The drug also inhibits the cytopathic effect of HTLV-IIIIB (a virus derived from a pool of American patients) and HTLV-III/RF-11 (an isolate obtained from a Haitian patient that differs by about 20% in the amino acid sequence of the envelope gene from several isolates of HTLV-III/LAV, including HTLV-IIIIB, analyzed so far). 3'-Azido-3'-deoxythymidine also completely blocks viral replication as assessed by reverse transcriptase production in normal human peripheral blood mononuclear cells exposed to HTLV-IIIIB. Finally, at concentrations of 3'-azido-3'-deoxythymidine that block the in vitro infectivity and cytopathic effect of HTLV-IIIIB, the in vitro immune functions of normal T cells remain basically intact.

=> s guillet J?/au or guichard G?/au or ostankovitch M?/au or Connan F?/au or Quesnel A?/au or Chaoppin J?/au or Briand J?/au or muller S?/au
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The truncation symbol ? may be used only at the end of a search term. To specify a variable character within a word use '?', e.g., 'woman?' to search for both 'woman' and 'women'. Enter 'HELP TRUNCATION' at an arrow prompt (=>) for more information.

=> s guillet J?/au or guichard G?/au or ostankovitch M?/au or Connan F?/au or Quesnel A?/au or Chaoppin J?/au or Briand J?/au or muller S?/au
L20 8085 GUILLET J?/AU OR GUICHARD G?/AU OR OSTANKOVITCH M?/AU OR CONNAN F?/AU OR QUESNEL A?/AU OR CHAOPPIN J?/AU OR BRIAND J?/AU OR MULLER S?/AU

=> s l20 and peptide?
L21 1211 L20 AND PEPTIDE?

=> s l21 and (GAG OR ENV)
L22 58 L21 AND (GAG OR ENV)

=> s l21 and (GAG OR NEP)
L23 79 L21 AND (GAG OR NEP)

=> dup rem l23
PROCESSING COMPLETED FOR L23
L24 26 DUP REM L23 (53 DUPLICATES REMOVED)

=> s l24 and analogue?
L25 0 L24 AND ANALOGUE?

=> dis l24 1-26 ibib abs

L24 ANSWER 1 OF 26 MEDLINE MEDLINE DUPLICATE 1
ACCESSION NUMBER: 2001253996 MEDLINE
DOCUMENT NUMBER: 21240681 PubMed ID: 11342637
TITLE: Characteristics of HIV-1 Nef regions containing multiple CD8+ T cell epitopes: wealth of HLA-binding motifs and sensitivity to proteasome degradation.
AUTHOR: Choppin J; Cohen W; Bianco A; Briand J P; Connan F; Dalod M; Guillet J G
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies infectieuses et tumorales, Institut National de la Sante et de la Recherche Medicale, Unite 445, Institut Cochin de Genetique Moleculaire, Universite Rene Descartes, Paris, France..
SOURCE: JOURNAL OF IMMUNOLOGY, (2001 May 15) 166 (10) 6164-9.
JOURNAL code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
FILE SEGMENT: English
ENTRY MONTH: Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: 200108
Entered STN: 20010813
Last Updated on STN: 20010813
Entered Medline: 20010809

AB First and foremost among the many factors that influence epitope presentation are the degradation of Ag, which results in peptide liberation, and the presence of HLA class I molecules able to present the peptides to T lymphocytes. To define the regions of HIV-1 Nef that can provide multiple T cell epitopes, we analyzed the Nef sequence and determined that there are 73 peptides containing 81 HLA-binding motifs. We tested the binding of these peptides to six common HLA molecules (HLA-A2, -A3, -A24, -B7, -B8, and -B35), and we showed that most of them were efficient binders (54% of motifs), especially peptides associating with HLA-A3, -B7/35, and -B8 molecules. Nef peptides most frequently recognized by T cells of HIV-1-infected individuals were 90-97, 135-143,

71-81, 77-85, 90-100, 73-82, and 128-137. The frequency of T cell recognition was not directly related to the strength of peptide-HLA binding. The generation of Nef epitopes is crucial; therefore, we investigated the digestion by the 20S proteasome of a large peptide, Nef(66-100). This fragment was efficiently cleaved, and MH(2)-terminally extended precursors of epitope 71-81 were recognized by T cells of an HIV-1-infected individual. These results suggest that a high frequency of T cell recognition may depend on proteasome cleavage.

L24 ANSWER 2 OF 26 MEDLINE DUPLICATE 2
 ACCESSION NUMBER: 2001554913 MEDLINE
 DOCUMENT NUMBER: 21487849 PubMed ID: 11602047
 TITLE: Downregulation of major histocompatibility class I on human dendritic cells by HIV Nef impairs antigen presentation to HIV-specific CD8+ T lymphocytes.
 AUTHOR: Andrieu M; Chassin D; Desoutter J F; Bouchaert I; Baillet M; Hanau D; Guillet J G; Hosmalin A
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumoraes, INSERM U445, 27 rue du Fbg St-Jacques, 75014 Paris, France.
 SOURCE: AIDS RESEARCH AND HUMAN RETROVIRUSES, (2001 Sep 20) 17 (14) 1365-70.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 200112
 ENTRY DATE: Entered STN: 20011017
 Last Updated on STN: 20020222
 Entered Medline: 20011207

AB The HIV early regulatory Nef protein downregulates surface expression of major histocompatibility class I (MHC I) molecules on various immortalized cell lines and on T lymphocytes. MHC I-restricted presentation induces CD8+ T cell responses, which have a major role in limiting HIV infection. Induction of primary immune responses requires dendritic cells, which are major candidates as the first cells that can internalize the virus and present it to T cells in mucosal contamination. To test the effect of Nef on MHC I-restricted antigen presentation by dendritic cells, we used recombinant vaccinia viruses. Flow cytometric analysis of double labeling for a vaccinia protein and MHC I showed that HIV-1 Lai Nef indeed downregulated MHC I surface expression on dendritic cells. MHC I-restricted presentation to a Nef-specific CD8+ cell clone from an infected patient was decreased in an interferon gamma ELISpot assay. Presentation of a reverse transcriptase epitopic peptide on sorted Nef-infected cells was decreased in a peptide concentration-dependent way, confirming the role of MHC I downregulation in the impairment of the CD8+ cell-specific response. Therefore, Nef downregulates MHC I surface expression on human dendritic cells, impairing presentation to HIV-specific CD8+ cells. This action of Nef probably induces a deleterious delay in the early CD8+ responses during the first days of infection and at the onset of new viral mutants.

L24 ANSWER 3 OF 26 MEDLINE DUPLICATE 3
 ACCESSION NUMBER: 2001401183 MEDLINE
 DOCUMENT NUMBER: 21318631 PubMed ID: 11426068
 TITLE: Lipopeptides induce cell-mediated anti-HIV immune responses in seronegative volunteers.
 AUTHOR: Pialoux G; Gahery-Segard H; Sermet S; Poncelet H; Fournier S; Gerard L; Tartar A; Gras-Masse H; Levy J P; Guillet J G
 CORPORATE SOURCE: Hopital Rothschild, Paris, France. (ANRS VAC 04 Study Team). gilles.pialoux@rth.ap-hop-paris.fr
 SOURCE: AIDS, (2001 Jul 6) 15 (10) 1239-49.
 PUB. COUNTRY: England; United Kingdom
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 200108
 ENTRY DATE: Entered STN: 20010813
 Last Updated on STN: 20010813
 Entered Medline: 20010809

AB OBJECTIVE: Test the efficacy of a mixture of six NEF (N1, N2, N3), GAG (G1, G2) and ENV (E) lipopeptides in the induction of B- and T-cell anti-HIV responses. DESIGN: A randomized phase I open-label dose-finding trial. Twenty-eight healthy seronegative volunteers received the lipopeptides, with or without the adjuvant QS21. METHODS: Anti-HIV-peptide antibodies were detected by enzyme-linked immunosorbent assay and Western blotting. Induction of cellular responses was assessed by proliferative test and (51)Cr-release assay. RESULTS: Local and systemic adverse reactions were always mild or moderate. After three injections an antibody response was detected in 25 out of 28 volunteers (89%). T cells from 19 (79%) of the 24 volunteers proliferated in response to at least one peptide. The majority of the volunteers had induced a multispecific proliferative response; that is, cells from volunteers proliferated to two (five of 19), three (five of 19), four (three of 19) or five peptides (one of 19). Cytotoxic responses by anti-HIV CD8+ lymphocytes could be tested in 24 volunteers, 13 (54%) of whom had clear and reproducible responses, with strong activity in the remaining 12 (> 20% of specific lysis), and polypeptidic responses were detected in at least seven of the 13 responders. Cytotoxic responses were found against the whole NEF protein (clade B LAI) in three of four tested volunteers and cross-reactions with the proteins of clade B (MN) and clade A (Bangui) HIV-1 strains, and also HIV-2 ROD, were detected in one of two tested volunteers. CONCLUSIONS: Lipopeptides are promising immunogens for an AIDS vaccine.

L24 ANSWER 4 OF 26 MEDLINE DUPLICATE 4
 ACCESSION NUMBER: 2001133497 MEDLINE
 DOCUMENT NUMBER: 21066732 PubMed ID: 11145897
 TITLE: DNA vaccination of macaques with several different Nef sequences induces multispecific T cell responses.
 AUTHOR: Couillin I; Letourneur F; Lefebvre P; Guillet J G
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumoraes, INSERM U445, Paris, France.

SOURCE: VIROLOGY, (2001 Jan 5) 279 (1) 136-45.
 Journal code: 0110674. ISSN: 0042-6822.
 PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200103
 ENTRY DATE: Entered STN: 20010404
 Last Updated on STN: 20010404
 Entered Medline: 20010301

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary human immunodeficiency virus-1 and in maintaining disease-free infection. It has recently been shown that DNA immunization of rhesus monkeys can elicit strong, long-lived antigen-specific cytotoxic T lymphocyte (CTL) responses. In previous work, it was shown that macaque CTL responses to lipopeptide vaccination were directed against a limited number of epitopes. In the present study, we used the DNA immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six plasmids reflecting the variability of Nef epitopic regions in the simian immunodeficiency virus (SIV) mac251 primary isolate. The Nef genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that DNA immunization with Nef sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of Nef. Reacting T cell lines were expanded in vitro and multispecific CTL responses mapping the 96-138 Nef region were analyzed. Several peptides recognized by CTL were identified and studies using peptides reflecting the variability of Nef indicated that all of the Nef variants were recognized in the 96-138 region. Moreover, CTL responses were directed against an immunodominant epitope located in a functional region within the Nef protein that is essential for viral replication. This work shows that our approach of DNA immunization with several sequences induced multispecific T cell responses recognizing variants included in the SIVmac251 primary isolate.
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L24 ANSWER 5 OF 26 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 2000:881190 CAPLUS
 DOCUMENT NUMBER: 134:41099
 TITLE: Polypeptidic peptides derived from the Nef protein of HIV-1 for vaccine use
 INVENTOR(S): Choppin, Jeannine; Bourgault, Villada Isabelle; Guillet, Jean-Gerard; Connan, Francine; Perrier, Estelle
 PATENT ASSIGNEE(S): Biovector Therapeutics, Pr.; Institut National De La Sante Et De La Recherche Medicale-Inserm; Bourgault Villada, Isabelle
 SOURCE: PCT Int. Appl., 40 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 2
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075181	A1	20001214	WO 2000-FR1514	20000531
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794370	A1	20001208	FR 1999-7012	19990603
EP 1181314	A1	20020227	EP 2000-936995	20000531
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: FR 1999-7012 A 19990603
 WO 2000-FR1514 W 20000531

AB The invention relates to the use of polypeptidic fragments of a detd. protein for the prodn. of medicaments designed to prevent or treat pathologies in which said protein is recognized by the cellular immune system and said polypeptidic fragments are chosen from the HIV Nef protein. The invention also relates to polypeptidic proteinic fragments of the HIV Nef protein, a method for the prodn. and use thereof, esp. in the field of vaccination.

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 6 OF 26 MEDLINE DUPLICATE 5
 ACCESSION NUMBER: 2000111287 MEDLINE
 DOCUMENT NUMBER: 20111287 PubMed ID: 10644339
 TITLE: Multiepitopic B- and T-cell responses induced in humans by a human immunodeficiency virus type 1 lipopeptide vaccine.
 AUTHOR: Gahery-Segard H; Pialoux G; Charmateau B; Sermet S; Poncelet H; Raux M; Tartar A; Levy J P; Gras-Masse H; Guillet J G
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM Unit e 445, Institut Cochin de Gen etique Mol eculaire, Universit e Ren ee Descartes, H opital Cochin, 75014 Paris, France.. gahery@icgm.cochin.inserm.fr
 SOURCE: JOURNAL OF VIROLOGY, (2000 Feb) 74 (4) 1694-703.
 Journal code: 0113724. ISSN: 0022-538X.
 PUB. COUNTRY: United States
 (CLINICAL TRIAL)
 (CLINICAL TRIAL, PHASE I)
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 200003
 ENTRY DATE: Entered STN: 20000314
 Last Updated on STN: 20000314
 Entered Medline: 20000302

AB We have attempted to develop an anti-human immunodeficiency virus (HIV) lipopeptide vaccine with several HIV-specific long peptides modified by C-terminal addition of a single palmitoyl chain. A mixture of six lipopeptides derived from regulatory or structural HIV-1 proteins (

Nef, Gag, and Env) was prepared. A phase I study was conducted to evaluate immunogenicity and tolerance in lipopeptide vaccination of HIV-1-seronegative volunteers given three injections of either 100, 250, or 500 microg of each lipopeptide, with or without immunoadjuvant (QS21). This report analyzes in detail B- and T-cell responses induced by vaccination. The lipopeptide vaccine elicited strong and multi-epitopic B- and T-cell responses. Vaccinated subjects produced specific immunoglobulin G antibodies that recognized the Nef and Gag proteins. After the third injection, helper CD4(+) T-cell responses as well as specific cytotoxic CD8(+) T cells were also obtained. These CD8(+) T cells were able to recognize naturally processed viral proteins. Finally, specific gamma interferon-secreting CD8(+) T cells were also detected ex vivo.

L24 ANSWER 7 OF 26 MEDLINE DUPLICATE 6
 ACCESSION NUMBER: 2001102747 MEDLINE
 DOCUMENT NUMBER: 20569537 PubMed ID: 11118377
 TITLE: Temporal loss of Nef-epitope CTL recognition following macaque lipopeptide immunization and SIV challenge.
 AUTHOR: Mortara L; Letourneur F; Villefroy P; Beyer C; Gras-Masse H; Guillet J G; Bourgault-Villada I
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumoraux, Institut Cochin de Genetique Moleculaire (ICGM), INSERM U445, 27 rue du Faubourg Saint-Jacques, Paris, 75014, France.
 SOURCE: VIROLOGY, (2000 Dec 20) 278 (2) 551-61.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 200101
 ENTRY DATE: Entered STN: 20010322
 Last Updated on STN: 20010322
 Entered Medline: 20010126

AB To address the subtle interactions between antiviral cytotoxic T-cell (CTL) immune responses and the evolution of viral quasispecies variants in vivo, we performed a longitudinal study in a simian immunodeficiency virus (SIV)-infected rhesus macaque that had a long experimental SIV infection before developing simian AIDS. Before being infected with SIV, this animal was immunized with a mixture of seven lipopeptides derived from SIV Nef and Gag proteins and showed a bispecific antiviral CTL response directed toward Nef 169-178 and 211-225 peptides. After SIV infection, CTL activity against the Nef 169-178 epitope was no longer detectable, as assessed from peripheral blood mononuclear cells stimulated by autologous SIV. CTL activity against the 211-225 epitope was lost after 3 months, and an additional CTL response to the amino acids 112-119 Nef epitope emerged. Analysis of the Nef proviral sequence revealed the presence of immune escape variants first in the 211-225 epitope and much later in the 112-119 epitope. In contrast, epitope 169-178 showed only two mutations among all viral sequencing performed. We conclude that in this macaque, bispecific CTL exerted a strong selective pressure and escape virus mutants finally emerged. We identified CTL recognizing a conserved Nef epitope 112-119 (SYKLALDM), essential for viral replication, which could be associated with a prolonged AIDS-free period. These results stress the importance of the induction of broader multispecific CTLs directed against highly conserved and functional T-cell epitopes by vaccination, with the aim of keeping HIV infection in check.
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L24 ANSWER 8 OF 26 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1999:659413 CAPLUS
 DOCUMENT NUMBER: 131:270954
 TITLE: Lipopeptides inducing cytotoxic T lymphocytes cytotoxicity and bearing at least one auxiliary T epitope with improved solubility for use in vaccines
 INVENTOR(S): Le Gal, Frederique Anne; Guillet, Jean Gerard ; Gahery-Segard, Hanne; Gras-Masse, Helene; Melnyk, Oleg; Tartar, Andre
 PATENT ASSIGNEE(S): Institut National de la Sante et de la Recherche Medicale INSERM, Fr.; Centre National de la Recherche Scientifique; Institut Pasteur de Lille
 SOURCE: PCT Int. Appl., 67 pp.
 CODEN: PIXXD2
 DOCUMENT TYPE: Patent
 LANGUAGE: French
 FAMILY ACC. NUM. COUNT: 1
 PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9951630	A1	19991014	WO 1999-FR792	19990406
W:	AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM			
RM:	GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG			
FR 2776926	A1	19991008	FR 1998-4323	19980407
CA 2328294	AA	19991014	CA 1999-2328294	19990406
AU 9930413	A1	19991025	AU 1999-30413	19990406
EP 1068226	A1	20010117	EP 1999-911884	19990406
R:	AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI			
JP 2002512941	T2	20020508	JP 2000-542351	19990406
PRIORITY APPLN. INFO.:			FR 1998-4323 A	19980407
			WO 1999-FR792 W	19990406

AB Lipopeptides carrying cytotoxic T lymphocyte epitopes and auxiliary T cell epitopes that have good soly. and that can be used in vaccines are described. The peptides have the epitopes and the lipid-binding domains sepd. by hydrophilic peptides (1-10, preferably 2-4 residues) rich in amino acids carrying charges at neutral pH, particularly arginine. The peptides may be conventional linear peptides or the hydrophilic peptides may be used to crosslink peptides via side chains. Such peptides may be used in vaccines inducing an immune response against HIV and BHV, papillomavirus, melanoma p53, or malaria. Palmitoylated peptides carrying an auxiliary epitope of tetanus toxin and a cytotoxic

T-lymphocyte epitope of the MART-1 receptor recognized by HLA A2.1 were synthesized. One peptide using an alanine spacer was practically insol. in water, while others with improved soly. had spacers contg. arginine and glycine were sol. The peptides stimulated secretion of interferon .gamma. from cytotoxic T lymphocytes responding to the MART-1 epitope and the monopalmitoylated peptide was more effective than the epitope alone or a dipalmitoylated peptide. Tests with T cells from HIV-infected patients indicated that multi-epitopic lipopeptides were recognized by individuals with expressing different class I HLA antigens.

REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L24 ANSWER 9 OF 26 MEDLINE DUPLICATE 7
 ACCESSION NUMBER: 1999214387 MEDLINE
 DOCUMENT NUMBER: 99214387 PubMed ID: 10196344
 TITLE: Type 1 CD4(+) T-cell help is required for induction of antipeptide multispecific cytotoxic T lymphocytes by a lipopeptidic vaccine in rhesus macaques.
 AUTHOR: Mortara L; Gras-Masse H; Rommens C; Venet A; Guillet J G; Bourgault-Villada I
 CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445-Universite Rene Descartes, Hopital Cochin, 75014 Paris, France.mortara@cochin.inserm.fr
 SOURCE: JOURNAL OF VIROLOGY, (1999 May) 73 (5) 4447-51. Journal code: 0113724. ISSN: 0022-538X.
 PUB. COUNTRY: United States
 LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
 FILE SEGMENT: English
 ENTRY MONTH: Priority Journals; AIDS
 ENTRY DATE: 199905
 ENTRY DATE: Entered STN: 19990601
 Last Updated on STN: 19990601
 Entered Medline: 19990519

AB We have optimized the induction of antiviral cytotoxic T lymphocytes (CTL) in rhesus macaques by a lipopeptide vaccine containing seven peptides from simian immunodeficiency virus (SIV) Nef and Gag proteins and a strong T-helper peptide from tetanus toxoid (TT) that is promiscuous in humans (peptide TT 830-846). Two of the eight immunized macaques showed T-helper (Th) cell proliferation and a specific synthesis of gamma interferon in response to TT 830-846 peptide. They also showed multispecific cytotoxic activity against three to five of the immunizing SIV peptides. These results show the importance of a strong specific type 1 Th response for inducing a multispecific CTL response in vivo, which is essential for the development of an anti-human immunodeficiency virus vaccine.

L24 ANSWER 10 OF 26 MEDLINE DUPLICATE 8
 ACCESSION NUMBER: 2000029790 MEDLINE
 DOCUMENT NUMBER: 20029790 PubMed ID: 10562305
 TITLE: Weak anti-HIV CD8(+) T-cell effector activity in HIV primary infection.
 AUTHOR: Dalod M; Dupuis M; Deschemin J C; Goujard C; Deveau C; Meyer L; Ngo N; Rouzioux C; Guillet J G; Delfrayssy J P; Sinet M; Venet A
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Unite Institut National de la Sante et de la Recherche Medicale (INSERM) 445, Institut Cochin de Genetique Moleculaire, Universite Rene Descartes, 75014 Paris, France.
 SOURCE: JOURNAL OF CLINICAL INVESTIGATION, (1999 Nov) 104 (10) 1431-9. Journal code: 7802877. ISSN: 0021-9738.
 PUB. COUNTRY: United States
 LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
 FILE SEGMENT: English
 ENTRY MONTH: Abridged Index Medicus Journals; Priority Journals; AIDS
 ENTRY DATE: 199912
 ENTRY DATE: Entered STN: 20000113
 Last Updated on STN: 20000113
 Entered Medline: 19991209

AB HIV-specific CD8(+) T cells play a major role in the control of virus during HIV primary infection (PI) but do not completely prevent viral replication. We used IFN-gamma enzyme-linked immunospot assay and intracellular staining to characterize the ex vivo CD8(+) T-cell responses to a large variety of HIV epitopic peptides in 24 subjects with early HIV PI. We observed HIV-specific responses in 71% of subjects. Gag and Nef peptides were more frequently recognized than Env and Pol peptides. The number of peptides recognized was low (median 2, range 0-6). In contrast, a much broader response was observed in 30 asymptomatic subjects with chronic infection: all were responders with a median of 5 peptides recognized (range 1-13). The frequency of HIV-specific CD8(+) T cells among PBMC for a given peptide was of the same order of magnitude in both groups. The proportion of HIV-specific CD8(+)CD28(-) terminally differentiated T cells was much lower in PI than at the chronic stage of infection. The weakness of the immune response during HIV PI could partially account for the failure to control HIV. These findings have potential importance for defining immunotherapeutic strategies and establishing the goals for effective vaccination.

L24 ANSWER 11 OF 26 MEDLINE DUPLICATE 9
 ACCESSION NUMBER: 1999129881 MEDLINE
 DOCUMENT NUMBER: 99129881 PubMed ID: 9933101
 TITLE: Dendritic cells transfected with the nef genes of HIV-1 primary isolates specifically activate cytotoxic T lymphocytes from seropositive subjects.
 AUTHOR: Chassin D; Andrieu M; Cohen W; Culmann-Penciolelli B; Ostankovitch M; Hanau D; Guillet J G
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, ICGM, Universite Rene Descartes, Paris, France.. chassin@icgm.cochin.inserm.fr
 SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1999 Jan) 29 (1) 196-202. Journal code: 1273201. ISSN: 0014-2980.
 PUB. COUNTRY: GERMANY; Federal Republic of
 LANGUAGE: Journal; Article; (JOURNAL ARTICLE)
 FILE SEGMENT: English
 ENTRY MONTH: Priority Journals; AIDS
 ENTRY DATE: 199902
 ENTRY DATE: Entered STN: 19990301
 Last Updated on STN: 19990301
 Entered Medline: 19990216

AB The HIV-1 Nef protein down-modulates surface expression of MHC class I proteins. Primary infected T lymphocytes thus escape lysis by cytotoxic T lymphocytes (CTL). In contrast, during HIV-1 infection there are strong CTL responses to several HIV proteins, and there is mounting evidence that CTL are critical for controlling the virus. The present study was carried out to assess Nef protein-cell interaction as it occurs in naturally infected antigen-presenting cells. To evaluate the presentation of peptides derived from viral antigen to CTL, we transfected nef genes obtained from peripheral blood mononuclear cells of HIV-1-seropositive subjects into dendritic cells isolated from monocytes of healthy donors. We demonstrate that expression and subsequent processing of Nef by transfected dendritic cells did not alter the presentation of an immunodominant epitope of Nef to CTL of HIV+ subjects. However, mutations in nef gene sequences from primary isolates may abolish this presentation by a mechanism that probably interferes with protein processing.

L24 ANSWER 12 OF 26 MEDLINE MEDLINE DUPLICATE 10
 ACCESSION NUMBER: 1998105786 MEDLINE
 DOCUMENT NUMBER: 98105786 PubMed ID: 9445041
 TITLE: Selection of virus variants and emergence of virus escape mutants after immunization with an epitope vaccine.
 AUTHOR: Mortara L; Letourneur P; Gras-Masse H; Venet A; Guillet J G; Bourgault-Villard I
 CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France..
 SOURCE: JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1403-10.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199802
 ENTRY DATE: Entered STN: 19980226
 Last Updated on STN: 19980226
 Entered Medline: 19980218

AB In this report, we assessed the evolution of the cytotoxic T-lymphocyte (CTL) response induced by an epitope vaccine. In two macaques immunized with a mixture of lipopeptides derived from simian immunodeficiency virus (SIV) Nef and Gag proteins, CTL responses were directed against the same, single epitope of the Nef protein (amino acids 128 to 137) presenting an alanine at position 136 (Nef 128-137/136A). However, after 5 months of SIV infection, peripheral blood mononuclear cells from both macaques lost their ability to be stimulated by autologous SIV-infected cells while still retaining their capacity to generate cytotoxic responses after specific Nef 128-137/136A peptide stimulation. The sequences of the pathogenic viral isolate used for the challenge showed a mixture of several variants. Within the Nef epitopic sequence from amino acids 128 to 137, 82% of viral variants expressed the epitopic peptide Nef 128-137/136A; the remaining variants presented a threonine at position 136 (Nef 128-137/136T). In contrast, sequence analysis of cloned proviral DNA obtained from both macaques 5 months after SIV challenge showed a different pattern of quasi-species variants; 100% of clones presented a threonine at position 136 (Nef 128-137/136T), suggesting the disappearance of viral variants with an alanine at this position under antiviral pressure exerted by Nef 128-137/136A-specific CTLs. In addition, 12 months after SIV challenge, six of eight clones from one macaque presented a glutamic acid at position 131 (Nef 128-137/131E-136T), which was not found in the infecting isolate. Furthermore, CTLs generated very early after SIV challenge were able to lyse cells sensitized with the Nef 128-137/136A epitope. In contrast, lysis was significantly less effective or even did not occur when either the selected peptide Nef 128-137/136T or the escape variant peptide Nef 128-137/131E+136T was used in a target cell sensitization assay. Dose analysis of peptides used to sensitize target cells as well as a major histocompatibility complex (MHC)-peptide stability assay suggested that the selected peptide Nef 128-137/136T has an altered capacity to bind to the MHC. These data suggest that CTL pressure leads to the selection of viral variants and to the emergence of escape mutants and supports the fact that immunization should elicit broad CTL responses.

L24 ANSWER 13 OF 26 CAPLUS COPYRIGHT 2002 ACS
 ACCESSION NUMBER: 1996.433011 CAPLUS
 DOCUMENT NUMBER: 125.112540
 TITLE: Among all human T-cell leukemia virus type 1 proteins, tax, polymerase, and envelope proteins are predicted as preferential targets for the HLA-A2-restricted cytotoxic T-cell response
 AUTHOR(S): Pique, Claudine; Connan, Francine; Levilain, Jean-Pierre; Chopin, Jeannine; Dokhelar, Marie-Christine
 CORPORATE SOURCE: URA 1156 CNRS and Service Immuno-Hematologie, Inst. Gustave Roussy, Paris, Fr.
 SOURCE: J. Virol. (1996), 70(8), 4919-4926
 CODEN: JOVIAM; ISSN: 0022-538X
 DOCUMENT TYPE: Journal
 LANGUAGE: English

AB The human T-cell leukemia virus type 1 (HTLV-1) is a human retrovirus assocd. with two diseases for which no successful treatment is yet available; the development of a vaccine is therefore an important issue. Since HTLV-1 is a persistent virus, an efficient vaccine will probably require a cytotoxic T-lymphocyte (CTL) response in addn. to the prodn. of antibodies. To identify potential CTL epitopes, we have selected, within all of the HTLV-1 proteins, nonapeptides contg. anchor residues required for assocn. with HLA-A2 mols. (residues at positions 2 and 9), which is the most frequently occurring A allele in all human populations. A set of 111 peptides was synthesized and tested in vitro in two assembly assays using processing-defective T2 cells. Anchor motifs selected were those contg. two major anchor residues (L2/M2/K2-/V9/L9/I9) (one letter amino-acid code) and those including tolerated anchor residues (V2/A2/T2 and/or A9/M9/T9). The anal. of the binding capacity of the peptides confirms the high efficiency of the L2-V9 anchor motif and shows that a systematic research of potential binding peptides should exclude peptides contg. known detrimental residues rather than select only peptides with known favored residues. We show that 39 peptides representative of all the HTLV-1 proteins are able to bind to HLA-A2 mols. Strong binder peptides which are very likely good CTL epitopes were identified in three HTLV-1 proteins, Tax, envelope, and polymerase. Three of the strong binder

peptides correspond to previously described HLA-A2-restricted CTL epitopes in the Tax protein, and two others are localized in a domain of the viral envelope recognized by natural neutralizing antibodies. This latter result has important implications for the development of an anti-HTLV-1 vaccine.

L24 ANSWER 14 OF 26 MEDLINE DUPLICATE 11
 ACCESSION NUMBER: 95220421 MEDLINE
 DOCUMENT NUMBER: 95220421 PubMed ID: 7705402
 TITLE: HLA-dependent variations in human immunodeficiency virus Nef protein alter peptide/HLA binding.
 AUTHOR: Couillin I; Connan F; Culmann-Penciolelli B; Gomard E; Guillet J G; Choppin J
 CORPORATE SOURCE: Unite 152, Institut National de la Sante et de la Recherche Medicale, Institut Cochin de Genetique, Moleculaire, Paris, France.
 SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Mar) 25 (3) 728-32. Journal code: 1273201. ISSN: 0014-2980.
 PUB. COUNTRY: GERMANY: Germany, Federal Republic of Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199505
 ENTRY DATE: Entered STN: 19950518
 Last Updated on STN: 19970203
 Entered Medline: 19950509

AB In human immunodeficiency virus (HIV) infection, sequence variations within defined cytotoxic T lymphocyte (CTL) epitopes may lead to escape from CTL recognition. In a previous report, we have shown that the variable central region of HIV Nef protein (amino acids 73-144) that contains potential CTL epitopes, can escape the CTL response. We suggested that this non recognition occurs through a variety of mechanisms. In particular, we provided evidence that HIV Nef sequences recovered from HLA-A11-expressing individuals have alterations in the major anchor residues essential for binding of the two Nef epitopes (amino acids 73-82 and 84-92) to the HLA-A11 molecule. Here, we investigate in more detail whether variations in autologous Nef sequences affect HLA binding, leading to CTL escape. Potential epitopes were sought by testing Nef peptides containing the HLA-A11-specific motif or related motifs. We confirmed that only the two previously described epitopes identified in cytotoxicity tests have optimal reactivity with the HLA-A11 molecule. We then sequenced several viral variants from donors that do not express the HLA-A11 molecule and compared the variability of these epitopes with those obtained from HLA-A11-expressing individuals. One substitution (Leu85) found in the sequences isolated from both populations increase the reactivity of the HLA-A11-restricted epitope 84-92, and might explain the difference in immunogenicity observed between the two HLA-A11-restricted epitopes from HLA-A11+ individuals. In addition, selective variations were only detected in virus isolated from HLA-A11-expressing individuals. Furthermore, examination of the association of variant peptides with the HLA-A11 molecule demonstrated that a single substitution within the minimal epitope could not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to escape CTL recognition.

L24 ANSWER 15 OF 26 MEDLINE
 ACCESSION NUMBER: 95074927 MEDLINE
 DOCUMENT NUMBER: 95074927 PubMed ID: 7983767
 TITLE: Identification of multirestricted immunodominant regions recognized by cytolytic T lymphocytes in the human immunodeficiency virus type 1 Nef protein.
 AUTHOR: Culmann-Penciolelli B; Lamhamedi-Cherradi S; Couillin I; Guegan N; Levy J P; Guillet J G; Gomard E
 CORPORATE SOURCE: Laboratoire d'Immunologie des Interactions Cellulaires et Moleculaires Institut National de la Sante de la Recherche Medicale U152, Paris, France.
 SOURCE: JOURNAL OF VIROLOGY, (1995 Jan) 69 (1) 618. Journal code: 0113724. ISSN: 0022-538X.
 PUB. COUNTRY: United States
 LANGUAGE: Errata; (PUBLISHED ERRATUM)
 FILE SEGMENT: English
 ENTRY MONTH: Priority Journals; AIDS
 ENTRY DATE: 199501
 Entered STN: 19950116
 Last Updated on STN: 19950116
 Entered Medline: 19950105

L24 ANSWER 16 OF 26 MEDLINE
 ACCESSION NUMBER: 94266816 MEDLINE
 DOCUMENT NUMBER: 94266816 PubMed ID: 8206929
 TITLE: Two pairs of oppositely charged amino acids from Jun and Fos confer heterodimerization to GCN4 leucine zipper.
 AUTHOR: John M; Briand J P; Granger-Schnarr M; Schnarr M
 CORPORATE SOURCE: Institut de Biologie Moleculaire et Cellulaire du CNRS, UPR 9002, Strasbourg, France.
 SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, (1994 Jun 10) 269 (23) 16247-53. Journal code: 2985121R. ISSN: 0021-9258.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals
 ENTRY MONTH: 199407
 ENTRY DATE: Entered STN: 19940721
 Last Updated on STN: 19940721
 Entered Medline: 19940713

AB The preferential assembly of Jun and Fos into heterodimers has been shown to be mainly driven by 16 amino acids (8 from each protein) situated in positions e and g of the leucine zipper coiled-coil structures of the two proteins (O'Shea, E. K., Rutkowski, R., and Kim, P. S. (1992) Cell 68, 699-708). Using a similar approach, we show that among these residues two pairs of oppositely charged amino acids account in fact for most of the additional free energy of heterodimerization in this system. These residues are 2 glutamic acid side chains in positions g1 and e2 of the Fos leucine zipper and 2 lysine residues in the equivalent positions of the Jun zipper. These amino acids were placed in the context of a GCN4 leucine zipper using peptide synthesis. These peptides contain unique cysteine residues enabling the formation of covalent dimers. The gain in heterodimer free energy has been determined both by cysteine-linked dimer formation under redox conditions and by thermal melting experiments of covalent dimers using circular dichroism

experiments. The two pairs of oppositely charged residues (Glu, Glu and Lys, Lys) in positions g1 and e2 contribute at least -1.9 kcal/mol of additional free energy, accounting for a 50-fold excess of the heterodimer with respect to one of the homodimers. Thermal denaturation studies as a function of pH and ionic strength suggest that electrostatic effects should indeed be a major driving force for heterodimerization. On the contrary, peptides harboring the 12 amino acids from Jun and Fos in the other e and g positions (i.e. in e1, g2, e3, g3, e4, and g4) show only a moderate tendency to form heterodimers.

L24 ANSWER 17 OF 26 MEDLINE DUPLICATE 12
 ACCESSION NUMBER: 95018646 MEDLINE
 DOCUMENT NUMBER: 95018646 PubMed ID: 7523699
 TITLE: Identification of multirestricted immunodominant regions recognized by cytolytic T lymphocytes in the human immunodeficiency virus type 1 Nef protein.
 COMMENT: Erratum in: J Virol 1995 Jan;69(1):618
 AUTHOR: Culmann-Penciolelli B; Lamhamedi-Cherradi S; Couillin I; Guegan N; Levy J P; Guillet J G; Gomard E
 CORPORATE SOURCE: Laboratoire d'Immunologie des Interactions Cellulaires et Moleculaires, Institut National de la Sante et de la Recherche Medicale U152, Institut Cochin de Genetique Moleculaire, Paris, France.
 SOURCE: JOURNAL OF VIROLOGY, (1994 Nov) 68 (11) 7336-43.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199411
 ENTRY DATE: Entered STN: 19941222
 Last Updated on STN: 19970203
 Entered Medline: 19941117

AB Peripheral blood mononuclear cells from a large number of human immunodeficiency virus (HIV)-seropositive donors were used to analyze the CD8+ T-cell response to each part of the Nef protein of HIV-1/LAI. This report identifies an immunodominant region (amino acids 73 to 144) in the Nef protein that was recognized by 97% of the NEF responder donors. This peptide sequence was dissected into four epitopic regions (amino acids 73 to 82, 83 to 97, 113 to 128, and 126 to 144), each of which was recognized under different HLA class I restrictions. Short overlapping peptides were used to sensitive the target cells for cytotoxicity and so to determine if these epitopic regions were multirestricted. Each region was found to contain several epitopes recognized with different HLA molecules. Thus, the central region of the Nef protein, a regulatory protein expressed early in HIV-infected cells, is rich in epitopic sequences which are found to be similar in many infected individuals and which can be recognized in association with at least ten HLA class I molecules. Their implications for the vaccination of humans with peptide sequences are discussed.

L24 ANSWER 18 OF 26 MEDLINE DUPLICATE 13
 ACCESSION NUMBER: 94179836 MEDLINE
 DOCUMENT NUMBER: 94179836 PubMed ID: 8133061
 TITLE: Simian immunodeficiency virus as a model for vaccination against HIV. Induction in rhesus macaques of GAG- or NEF-specific cytotoxic T lymphocytes by lipopeptides.
 AUTHOR: Bourgault I; Chirat F; Tartar A; Levy J P; Guillet J G; Venet A
 CORPORATE SOURCE: Cochin Institute of Molecular Genetics, Cochin Hospital, Paris, France.
 SOURCE: JOURNAL OF IMMUNOLOGY, (1994 Mar 1) 152 (5) 2530-7.
 PUB. COUNTRY: United States
 LANGUAGE: English
 FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
 ENTRY MONTH: 199404
 ENTRY DATE: Entered STN: 19940428
 Last Updated on STN: 19970203
 Entered Medline: 19940419

AB The protection against infection by HIV probably requires the induction of both neutralizing Abs and CTL responses. Vaccination by attenuated HIV is hardly acceptable and the use of viral genes inserted in recombinant living vectors needs further development, especially with respect to safety. The peptidic vaccination is a promising approach but free peptides are usually poorly immunogenic. Because potent immune responses have been obtained in mice with modified peptides such as lipopeptides, we have designed a study to assess the immunogenicity of lipopeptides in nonhuman primates. Seven lipopeptides were synthesized, derived from known immunogenic regions of the simian immunodeficiency virus (SIV) NEF and GAG proteins. Twelve rhesus macaques, randomly chosen and not selected on their MHC basis, were immunized subcutaneously with the seven lipopeptides in IPA. An MHC class I-restricted and CD(8+)-mediated CTL response has been observed in seven macaques directed against one or two of the synthetic immunizing peptides in each case. These CTLs were able to lyse autologous target cells infected with a recombinant vaccinia virus expressing the SIV nef or gag genes, suggesting that they recognized the naturally processed peptides. These activities are detectable in peripheral blood cells for at least 10 mo after the last immunization. Abs against the immunizing peptides have also been observed in all cases. This study demonstrates that lipopeptides can generate cytotoxic and humoral immune responses in a large number of unselected animals and this approach may thus be worth considering in the vaccination against HIV.

L24 ANSWER 19 OF 26 MEDLINE DUPLICATE 14
 ACCESSION NUMBER: 94342829 MEDLINE
 DOCUMENT NUMBER: 94342829 PubMed ID: 7520468
 TITLE: Impaired cytotoxic T lymphocyte recognition due to genetic variations in the main immunogenic region of the human immunodeficiency virus 1 NEF protein.
 COMMENT: Comment in: J Exp Med. 1994 Sep 1;180(3):779-82
 AUTHOR: Couillin I; Culmann-Penciolelli B; Gomard E; Choppin J; Levy J P; Guillet J G; Saragosti S
 CORPORATE SOURCE: Institut National de la Sante et de la Recherche Medicale, Unit *363, Paris, France.
 SOURCE: JOURNAL OF EXPERIMENTAL MEDICINE, (1994 Sep 1) 180 (3) 1129-34.
 Journal code: 2985109R. ISSN: 0022-1007.

PUB. COUNTRY: United States
 Journal; Article; (JOURNAL ARTICLE)
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199409
 ENTRY DATE: Entered STN: 19941005
 Last Updated on STN: 19970203
 Entered Medline: 19940922

AB Human immunodeficiency virus (HIV) induces strong responses from human histocompatibility leukocyte antigen (HLA) class I-restricted cytotoxic T lymphocytes (CTL). In a previous report we identified an immunodominant region (amino acids 73-144) in the Nef protein that was recognized by CD8+ class I-restricted CTL of most asymptomatic individuals. Analysis of the 73-144 region by peptide sensitization, experiments using overlapping peptides corresponding to the LAI isolate identified the peptide sequences located between residues 73 and 82 or 84 and 92 and the peptide sequence between residues 134 and 144 as cognate peptides for HLA-A11- and HLA-B18-restricted epitopes, respectively. This report describes the variable demonstrable reactivities of CTL obtained from HLA-A11 or HLA-B18 seropositive, asymptomatic patients who all had a response to the virus Nef protein, but who did not always recognize appropriate cognate peptides. The high mutation rate of HIV probably facilitates the selection of mutants that can avoid the cellular immune response. We therefore analyzed the variability of these epitopes restricted by HLA-A11 and HLA-B18. We sequenced several viral isolates from HLA-A11 and HLA-B18 donors who recognized certain HLA-peptide complexes and from those who did not. A CTL sensitization assay was used to show that some mutations led to a great reduction in CTL activity in vitro. This might be due to failure of the mutated epitope to bind major histocompatibility complex class I molecule. A simple assay was used to detect peptides that promoted the assembly of class I molecules. Some of these mutations at major anchor positions prevented HLA-A11/peptide binding, and consequently impaired recognition of the HLA-peptide complex by the T cell receptor.

L24 ANSWER 20 OF 26 MEDLINE MEDLINE DUPLICATE 15
 ACCESSION NUMBER: 94170859 MEDLINE
 DOCUMENT NUMBER: 94170859 PubMed ID: 8125145
 TITLE: A simple assay for detection of peptides promoting the assembly of HLA class I molecules.
 AUTHOR: Connan F; Hlavac F; Hoebeke J; Guillet J G; Choppin J
 CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM U152, Paris, France.
 SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1994 Mar) 24 (3) 777-80. Journal code: 1273201. ISSN: 0014-2980.
 PUB. COUNTRY: GERMANY; Germany, Federal Republic of
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199404
 ENTRY DATE: Entered STN: 19940420
 Last Updated on STN: 19940420
 Entered Medline: 19940412

AB Synthetic peptides derived from influenza virus and human immunodeficiency virus were tested for their ability to promote the assembly of HLA-A2 and HLA-B51 molecules in T2 cell lysates. Specific assembly was detected by an enzyme-linked immunosorbent assay. The most significant HLA-A2 assembly was obtained in the presence of peptides known to be targets for HLA-A2-restricted cytotoxic T lymphocytes (influenza matrix M.58-66 and HIV Pol 476-484). Three of a batch of Nef peptides corresponding to epitopic regions for cytotoxic T lymphocytes, caused significant assembly of HLA-A2 (Nef 83-91, 137-145 and 144-153), but only at high concentrations (100 microm). As these peptides bound relatively weakly, it is unlikely that they are good candidates for HLA-A2-restricted CTL epitopes. Peptides matrix M.60-68, Nef 186-194, and Plasmodium falciparum sh.77-85 produced the most significant assembly of HLA-B51. These peptides have a dominant hydrophobic anchor residue (V, L, I) at position 9 that could occupy pocket "P". Our results also suggest that another hydrophobic residue (V, L) at position 3 or 4 may anchor to hydrophobic pocket "D" of HLA-B51. Proline at position 2 greatly increases HLA-B51 anchoring.

L24 ANSWER 21 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1993:445486 BIOSIS
 DOCUMENT NUMBER: PREV199345081111
 TITLE: SIV as a model for vaccination against HIV: Induction by lipopeptides in rhesus macaques of GAG or Nef specific cytotoxic T lymphocytes (CTL).
 AUTHOR(S): Bourgault, I.; Chirat, F.; Tartar, A.; Guillet, J. G.; Levy, J. P.; Venet, A.
 CORPORATE SOURCE: ICGM, INSERM U152, Hopital Cochin, 27 rue du Faubourg Saint Jacques, 75014 Paris France
 SOURCE: IXTH INTERNATIONAL CONFERENCE ON AIDS AND THE IVTH STD WORLD CONGRESS.. (1993) pp. 253. IXth International Conference on AIDS in affiliation with the IVth STD World Congress. Publisher: IXth International Conference on AIDS Berlin, Germany. Meeting Info.: Meeting Berlin, Germany June 6-11, 1993
 DOCUMENT TYPE: Conference
 LANGUAGE: English

L24 ANSWER 22 OF 26 BIOSIS COPYRIGHT 2002 BIOLOGICAL ABSTRACTS INC.
 ACCESSION NUMBER: 1993:445267 BIOSIS
 DOCUMENT NUMBER: PREV199345080892
 TITLE: Detection of HLA-A2 and HLA-B5 peptide binding motifs in the HIV-1 Nef protein.
 AUTHOR(S): Connan, F.; Hlavac, F.; Guillet, J. G.; Choppin, J.
 CORPORATE SOURCE: ICGM, INSERM U152, Hopital Cochin, 27 rue du Fg St. Jacques, 75014 Paris France
 SOURCE: IXTH INTERNATIONAL CONFERENCE ON AIDS AND THE IVTH STD WORLD CONGRESS.. (1993) pp. 216. IXth International Conference on AIDS in affiliation with the IVth STD World Congress. Publisher: IXth International Conference on AIDS Berlin, Germany. Meeting Info.: Meeting Berlin, Germany June 6-11, 1993
 DOCUMENT TYPE: Conference

LANGUAGE: English

L24 ANSWER 23 OF 26 MEDLINE DUPLICATE 16
ACCESSION NUMBER: 93039645 MEDLINE
DOCUMENT NUMBER: 93039645 PubMed ID: 1384546
TITLE: HLA class I binding regions of HIV-1 proteins.
AUTHOR: Choppin J; Guillet J G; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM
U152, Paris, France.
SOURCE: CRITICAL REVIEWS IN IMMUNOLOGY, (1992) 12 (1-2) 1-16. Ref:
82
Journal code: 8914819. ISSN: 1040-8401.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199212
ENTRY DATE: Entered STN: 19930122
Last Updated on STN: 19970203
Entered Medline: 19921210

AB To identify HIV peptides containing HLA class I binding regions, different studies have been performed. These include the detection of interactions between HIV peptides and purified HLA molecules in solid-phase assays, the measurement of HLA molecule assembly in the presence of peptide added to cell lysates, and the detection of inhibition of CTL-mediated cytotoxicity by competition between peptides on target cells. To date, the HIV epitopes recognized by anti-HIV CTL are from the Env, Gag, Nef, and Pol proteins and they are identified using synthetic peptides of 12 to 20 amino acids. The search for a correlation between known HIV CTL epitopes and the results of HLA/peptide interaction assays reveals that: (1) most of the peptides that are positive in the assembly assay contain a HLA-A2 peptide motif but the correlation between these positive peptides and the CTL epitopes is not obvious; (2) a high proportion of HIV epitopes are included in the peptides positive in solid-phase binding and in inhibition of cytotoxicity assays, although these tests do not allow us to predict HLA restriction; (3) the HLA-A2 peptide motif is not systematically included in HLA-A2-restricted CTL epitopes, this observation raising the possibility that other sequences are involved in HLA binding.

L24 ANSWER 24 OF 26 MEDLINE DUPLICATE 17
ACCESSION NUMBER: 91302806 MEDLINE
DOCUMENT NUMBER: 91302806 PubMed ID: 1712812
TITLE: HLA-binding regions of HIV-1 proteins. II. A systematic study of viral proteins.
AUTHOR: Choppin J; Martinon F; Connan F; Pauchard M; Gomard E; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), INSERM
U152, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1991 Jul 15) 147 (2) 575-83.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910908
Last Updated on STN: 19970203
Entered Medline: 19910820

AB To detect HLA-binding peptides in 10 HIV-1 proteins (Rev, Tat, Vif, Vpr, Vpu, Gag p18, Gag p24, Gag p15, Env gp120 and Env gp41), the peptide binding assay (PBA) has been performed using three HLA class I molecules. Correlations have been searched between the PBA results and the peptide competitor activity in a functional test using HLA-A2-restricted CTL and target cells. A correlation between the data found in the PBA and well-defined CTL epitopes could be attempted only for the three Gag proteins. For these proteins, our results are in agreement with the known existence of epitopes reacting with human CD8+ CTL, with some exceptions. Together with the results reported with a panel of Nef peptides, these experiments showed that at least 18/20 of the already reported CTL epitopes from HIV-1 Gag, Nef, and Env proteins could be detected by the PBA, most (17/18) corresponding to strong reactivities. Perhaps more important, the regions of HIV-1 Gag p24 or Nef proteins that contain multiple associated CTL epitopes, with different HLA restrictions, were clearly identified by the reactivities in the PBA of several overlapping peptides and the major practical interest of the PBA might be the detection of such polyepitopic regions. Prediction are proposed in this report for 10 proteins, including several proteins for which CTL epitopes remain presently unknown.

L24 ANSWER 25 OF 26 MEDLINE DUPLICATE 18
ACCESSION NUMBER: 91302805 MEDLINE
DOCUMENT NUMBER: 91302805 PubMed ID: 1712811
TITLE: HLA-binding regions of HIV-1 proteins. I. Detection of seven HLA binding regions in the HIV-1 Nef protein.
AUTHOR: Choppin J; Martinon F; Connan F; Gomard E; Levy J P
CORPORATE SOURCE: Institut Cochin de Genetique Moleculaire (ICGM), Laboratoire d'Immunologie et Oncologie des Maladies, Retroviraes, INSERM U152, Paris, France.
SOURCE: JOURNAL OF IMMUNOLOGY, (1991 Jul 15) 147 (2) 569-74.
Journal code: 2985117R. ISSN: 0022-1767.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; AIDS
ENTRY MONTH: 199108
ENTRY DATE: Entered STN: 19910908
Last Updated on STN: 19970203
Entered Medline: 19910820

AB The physical association of HLA class I or H-2 molecules with 36 HIV-1 Nef synthetic peptides was studied using a direct peptide binding assay (PBA) in solid phase. To assess the functional significance of the PBA results, the Nef peptides were also tested for their ability to inhibit the lytic activity of human or murine CTL. The PBA results showed that seven partly overlapping regions of the Nef protein contained MHC binding peptides (4-18, 46-67, 73-94, 100-128, 126-155, 182-198, and

192-206). Five of these seven regions included all the already described epitopes recognized by CD8+ human CTL. The two other regions, 4-18 and 46-67, are not yet described as antigenic for human CD8+ cells but they are located in the N-terminal part of Nef that was previously described as being stimulator for rat or chimpanzee CD4+ cells. Altogether, it can be concluded that 1) In virtually 100% of the cases, the PBA is capable to detect known antigenic peptides recognized by CTL. 2) The PBA and the functional inhibition assay provide similar results, supporting the functional significance of PBA results. 3) The PBA is easy to handle on a large scale, using multiple peptide and several MHC molecules, so that it can be used as a routine method for prevision of possibly epitopic sequences. 4) Systematic studies of peptides issued from the whole sequence of a given protein allow to map polypeptidic areas that are probably the most interesting parts of proteins for a vaccine purpose.

L24 ANSWER 26 OF 26 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 1990:629080 CAPLUS

DOCUMENT NUMBER: 113:229080

TITLE: Analysis of physical interactions between peptides and HLA molecules and application to the detection of human immunodeficiency virus 1 antigenic peptides

AUTHOR(S): Choppin, Jeannine; Martinon, Frederic; Gomard, Elisabeth; Bahraoui, Elmostafa; Connan, Francine; Bouillot, Michel; Levy, Jean Paul

CORPORATE SOURCE: Hop. Cochin, Paris, 75014, Fr.

SOURCE: J. Exp. Med. (1990), 172(3), 889-99

CODEN: JEMEA; ISSN: 0022-1007

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The phys. assocn. of 40 antigenic peptides and purified HLA class I and class II mols. was monitored using a direct peptide binding assay (PBA) in solid phase and an inhibition peptide binding assay (IPBA) in which the competing peptide was present in a sol. phase. The ability was also examd. of different peptides to inhibit the lytic activity of human antiviral cytolytic T cells towards cells incubated with the corresponding target peptide. Binding of a given human T cell-recognized peptide to several HLA class I and class II mols. occurred frequently. Nevertheless, preferential binding of peptides to their resp. restriction mols. was also obsd. Binding of HLA mols. to peptides recognized by murine T cells occurred less frequently. Eleven of 24 (46%) randomly selected HIV-1 peptides contained agretopic residues allowing their binding to HLA mols. The kinetics of HLA/peptide assocn. depended on the peptide tested and were faster than or similar to those reported for Ia mols. Dissocn. of these complexes was very low. Peptide/HLA mol. binding was dependent on length, no. of pos. charges, and presence of hydrophobic residues in the peptide. A correlation was demonstrated between a peptide inhibitory effect in the IPBA and its blocking effect in the cytolytic test. The restriction phenomenon obsd. in T cell responses was not strictly related to either an elective HLA/peptide assocn., or a high binding capacity of a peptide to HLA mols. Also, the PBA and IPBA are appropriate for the detection of agretopic residues within HIV-1 proteins.

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(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002

L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
L3 207502 S ANALOGUE
L4 0 S L2 AND L3
L5 0 S L1 AND L3
L6 4675 S L3 AND HIV
L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
L8 184 S L7 (P) AIDS
L9 801 S L7 (P) (HIV OR NEF OR AIDS)
L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
L11 110 S L7 (P) (NEF OR GAG)
L12 64 S L11 AND PD-19980507
L13 41 DUP REM L12 (23 DUPLICATES REMOVED)
L14 800 S L7 (P) (HIV OR AIDS)
L15 575 S L14 NOT NUCLEO?
L16 262 S L15 AND PD-19980507
L17 244 S L16 NOT L13
L18 155 DUP REM L17 (89 DUPLICATES REMOVED)
L19 15 S L18 AND (NEF OR GAG)
L20 8085 S GUILLET J7/AU OR GUICHARD G7/AU OR OSTANKOVITCH M7/AU OR CONN
L21 1211 S L20 AND PEPTIDE?
L22 58 S L21 AND (GAG OR ENV)
L23 79 S L21 AND (GAG OR NEF)
L24 26 DUP REM L23 (53 DUPLICATES REMOVED)
L25 0 S L24 AND ANALOGUE?

--> s L24 and analogu?

L26 0 L24 AND ANALOGU?

--> s L24 and analog?

L27 0 L24 AND ANALOG?

--> s L24 and variant?

L28 4 L24 AND VARIANT?

--> s L24 and variant?

L29 4 L24 AND VARIANT?

--> s L24 and derivativ?

L30 0 L24 AND DERIVATIV?

--> dis L29 1-4 ibib abs

L29 ANSWER 1 OF 4

ACCESSION NUMBER: 2001133497 MEDLINE

DOCUMENT NUMBER: 21066732 PubMed ID: 11145897

TITLE: DNA vaccination of macaques with several different Nef sequences induces multispecific T cell responses.

AUTHOR: Couillin I; Letourneur P; Lefebvre P; Guillet J G

CORPORATE SOURCE: ; Martinon F
Laboratoire d'Immunologie des Pathologies Infectieuses et
Tumorales, INSERM U445, Paris, France.
SOURCE: VIROLOGY, (2001 Jan 5) 279 (1) 136-45.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010301

AB CD8(+) T lymphocytes play a key role in controlling viremia during primary human immunodeficiency virus-1 and in maintaining disease-free infection. It has recently been shown that DNA immunization of rhesus monkeys can elicit strong, long-lived antigen-specific cytotoxic T lymphocyte (CTL) responses. In previous work, it was shown that macaque CTL responses to lipopeptide vaccination were directed against a limited number of epitopes. In the present study, we used the DNA immunization approach to enlarge T cell responses to several epitopes and to multiple isolates. We immunized macaques with a mixture of six plasmids reflecting the variability of Nef epitope regions in the simian immunodeficiency virus (SIV) mac251 primary isolate. The Nef genes from viruses included in the SIVmac251 primary isolate were sequenced and the six selected sequences were individually subcloned into the pCI vector, under cytomegalovirus enhancer/promoter control, and injected into macaques. We show that DNA immunization with Nef sequences induced interferon-gamma (IFN-gamma) secreting cell responses directed against several regions of Nef. Reacting T cell lines were expanded in vitro and multispecific CTL responses mapping the 96-138 Nef region were analyzed. Several peptides recognized by CTL were identified and studies using peptides reflecting the variability of Nef indicated that all of the Nef variants were recognized in the 96-138 region. Moreover, CTL responses were directed against an immunodominant epitope located in a functional region within the Nef protein that is essential for viral replication. This work shows that our approach of DNA immunization with several sequences induced multispecific T cell responses recognizing variants included in the SIVmac251 primary isolate.
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L29 ANSWER 2 OF 4 MEDLINE
ACCESSION NUMBER: 2001102747 MEDLINE
DOCUMENT NUMBER: 20569537 PubMed ID: 11118377
TITLE: Temporal loss of Nef-epitope CTL recognition following macaque lipopeptide immunization and SIV challenge.
AUTHOR: Mortara L; Letourneur F; Villefroy P; Beyer C; Gras-Masse H; Guillet J G; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, Institut Cochin de Genetique Moleculaire (ICGM), INSERM U445, 27 rue du Faubourg Saint-Jacques, Paris, 75014, France.
SOURCE: VIROLOGY, (2000 Dec 20) 278 (2) 551-61.
Journal code: 0110674. ISSN: 0042-6822.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200101
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20010126

AB To address the subtle interactions between antiviral cytotoxic T-cell (CTL) immune responses and the evolution of viral quasiespecies variants in vivo, we performed a longitudinal study in a simian immunodeficiency virus (SIV)-infected rhesus macaque that had a long experimental SIV infection before developing simian AIDS. Before being infected with SIV, this animal was immunized with a mixture of seven lipopeptides derived from SIV Nef and Gag proteins and showed a bispecific antiviral CTL response directed toward Nef 169-178 and 211-225 peptides. After SIV infection, CTL activity against the Nef 169-178 epitope was no longer detectable, as assessed from peripheral blood mononuclear cells stimulated by autologous SIV. CTL activity against the 211-225 epitope was lost after 3 months, and an additional CTL response to the amino acids 112-119 Nef epitope emerged. Analysis of the Nef proviral sequence revealed the presence of immune escape variants first in the 211-225 epitope and much later in the 112-119 epitope. In contrast, epitope 169-178 showed only two mutations among all viral sequencing performed. We conclude that in this macaque, bispecific CTL exerted a strong selective pressure and escape virus mutants finally emerged. We identified CTL recognizing a conserved Nef epitope 112-119 (SYKLAIDM), essential for viral replication, which could be associated with a prolonged AIDS-free period. These results stress the importance of the induction of broader multispecific CTLs directed against highly conserved and functional T-cell epitopes by vaccination, with the aim of keeping HIV infection in check.
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L29 ANSWER 3 OF 4 MEDLINE
ACCESSION NUMBER: 1998105786 MEDLINE
DOCUMENT NUMBER: 98105786 PubMed ID: 9445041
TITLE: Selection of virus variants and emergence of virus escape mutants after immunization with an epitope vaccine.
AUTHOR: Mortara L; Letourneur F; Gras-Masse H; Venet A; Guillet J G; Bourgault-Villada I
CORPORATE SOURCE: Laboratoire d'Immunologie des Pathologies Infectieuses et Tumorales, INSERM U445, Paris, France..
mortara@icgm.cochin.inserm.fr
SOURCE: JOURNAL OF VIROLOGY, (1998 Feb) 72 (2) 1403-10.
Journal code: 0113724. ISSN: 0022-538X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980226
Last Updated on STN: 19980226
Entered Medline: 19980218

AB In this report, we assessed the evolution of the cytotoxic T-lymphocyte

(CTL) response induced by an epitope vaccine. In two macaques immunized with a mixture of lipopeptides derived from simian immunodeficiency virus (SIV) Nef and Gag proteins, CTL responses were directed against the same, single epitope of the Nef protein (amino acids 128 to 137) presenting an alanine at position 136 (Nef 128-137/136A). However, after 5 months of SIV infection, peripheral blood mononuclear cells from both macaques lost their ability to be stimulated by autologous SIV-infected cells while still retaining their capacity to generate cytotoxic responses after specific Nef 128-137/136A peptide stimulation. The sequences of the pathogenic viral isolate used for the challenge showed a mixture of several variants. Within the Nef epitopic sequence from amino acids 128 to 137, 82% of viral variants expressed the epitopic peptide Nef 128-137/136A; the remaining variants presented a threonine at position 136 (Nef 128-137/136T). In contrast, sequence analysis of cloned proviral DNA obtained from both macaques 5 months after SIV challenge showed a different pattern of quasi-species variants; 100% of clones presented a threonine at position 136 (Nef 128-137/136T), suggesting the disappearance of viral variants with an alanine at this position under antiviral pressure exerted by Nef 128-137/136A-specific CTLs. In addition, 12 months after SIV challenge, six of eight clones from one macaque presented a glutamic acid at position 131 (Nef 128-137/131E+136T), which was not found in the infecting isolate. Furthermore, CTLs generated very early after SIV challenge were able to lyse cells sensitized with the Nef 128-137/136A epitope. In contrast, lysis was significantly less effective or even did not occur when either the selected peptide Nef 128-137/136T or the escape variant peptide Nef 128-137/131E+136T was used in a target cell sensitization assay. Dose analysis of peptides used to sensitize target cells as well as a major histocompatibility complex (MHC)-peptide stability assay suggested that the selected peptide Nef 128-137/136T has an altered capacity to bind to the MHC. These data suggest that CTL pressure leads to the selection of viral variants and to the emergence of escape mutants and supports the fact that immunization should elicit broad CTL responses.

L29 ANSWER 4 OF 4 MEDLINE
 ACCESSION NUMBER: 95220421 MEDLINE
 DOCUMENT NUMBER: 95220421 PubMed ID: 7705402
 TITLE: HLA-dependent variations in human immunodeficiency virus Nef protein alter peptide/HLA binding.
 AUTHOR: Couillin I; Connan F; Culmann-Penciolelli B; Gomard E; Guillet J G; Chopin J
 CORPORATE SOURCE: Unite 152, Institut National de la Sante et de la Recherche Medicale, Institut Cochin de Genetique, Moleculaire, Paris, France.
 SOURCE: EUROPEAN JOURNAL OF IMMUNOLOGY, (1995 Mar) 25 (3) 728-32.
 PUB. COUNTRY: GERMANY; Germany, Federal Republic of
 LANGUAGE: English
 FILE SEGMENT: Priority Journals; AIDS
 ENTRY MONTH: 199505
 ENTRY DATE: Entered STN: 19950518
 Last Updated on STN: 19970203
 Entered Medline: 19950509

AB In human immunodeficiency virus (HIV) infection, sequence variations within defined cytotoxic T lymphocyte (CTL) epitopes may lead to escape from CTL recognition. In a previous report, we have shown that the variable central region of HIV Nef protein (amino acids 73-144) that contains potential CTL epitopes, can escape the CTL response. We suggested that this non recognition occurs through a variety of mechanisms. In particular, we provided evidence that HIV Nef sequences recovered from HLA-A11-expressing individuals have alterations in the major anchor residues essential for binding of the two Nef epitopes (amino acids 73-82 and 84-92) to the HLA-A11 molecule. Here, we investigate in more detail whether variations in autologous Nef sequences affect HLA binding, leading to CTL escape. Potential epitopes were sought by testing Nef peptides containing the HLA-A11-specific motif or related motifs. We confirmed that only the two previously described epitopes identified in cytotoxicity tests have optimal reactivity with the HLA-A11 molecule. We then sequenced several viral variants from donors that do not express the HLA-A11 molecule and compared the variability of these epitopes with those obtained from HLA-A11-expressing individuals. One substitution (Leu85) found in the sequences isolated from both populations increase the reactivity of the HLA-A11-restricted epitope 84-92, and might explain the difference in immunogenicity observed between the two HLA-A11-restricted epitopes from HLA-A11 individuals. In addition, selective variations were only detected in virus isolated from HLA-A11-expressing individuals. Furthermore, examination of the association of variant peptides with the HLA-A11 molecule demonstrated that a single substitution within the minimal epitope could not always completely abrogate HLA binding, suggesting that multiple alterations within a particular epitope may accumulate during disease progression, allowing the virus to escape CTL recognition.

--> dis his

(FILE 'HOME' ENTERED AT 12:18:33 ON 09 JUL 2002)

FILE 'MEDLINE, CAPLUS, EMBASE, BIOSIS' ENTERED AT 12:18:45 ON 09 JUL 2002

L1 20 S (NEF (1N) (84-92)) OR (GAG (1N) 77-85)
 L2 5 DUP REM L1 (15 DUPLICATES REMOVED)
 L3 207502 S ANALOGUE
 L4 0 S L2 AND L3
 L5 0 S L1 AND L3
 L6 4675 S L3 AND HIV
 L7 46831 S L3 (P) (PEPTIDE? OR PROTEIN?)
 L8 184 S L7 (P) AIDS
 L9 801 S L7 (P) (HIV OR NEF OR AIDS)
 L10 847 S L7 (P) (HIV OR NEF OR AIDS OR GAG)
 L11 110 S L7 (P) (NEF OR GAG)
 L12 64 S L11 AND PD<19980507
 L13 41 DUP REM L12 (23 DUPLICATES REMOVED)
 L14 800 S L7 (P) (HIV OR AIDS)
 L15 575 S L14 NOT NUCLEO?
 L16 262 S L15 AND PD<19980507
 L17 244 S L16 NOT L13
 L18 155 DUP REM L17 (89 DUPLICATES REMOVED)

L19 15 S L18 AND (NEF OR GAG)
 L20 8085 S GUILLET J?/AU OR GUICHARD G?/AU OR OSTANKOVITCH M?/AU OR CONN
 L21 1211 S L20 AND PEPTIDE?
 L22 58 S L21 AND (GAG OR ENV)
 L23 79 S L21 AND (GAG OR NEF)
 L24 26 DUP REM L23 (53 DUPLICATES REMOVED)
 L25 0 S L24 AND ANALOGUE?
 L26 0 S L24 AND ANALOGUE?
 L27 0 S L24 AND ANALOGUE?
 L28 4 S L24 AND VARIANT?
 L29 4 S L24 AND VARIANT?
 L30 0 S L24 AND DERIVATIV?

>> end

ALL L# QUERIES AND ANSWER SETS ARE DELETED AT LOGOFF

LOGOFF? (Y)/N/HOLD:y

COST IN U.S. DOLLARS

SINCE FILE	TOTAL
ENTRY	SESSION
299.44	299.65

FULL ESTIMATED COST

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)

SINCE FILE	TOTAL
ENTRY	SESSION
-2.48	-2.48

CA SUBSCRIBER PRICE

STN INTERNATIONAL LOGOFF AT 13:26:00 ON 09 JUL 2002